“TO INVESTIGATE THE PREVALENCE AND ASSOCIATION OF METABOLIC SYNDROME AND ITS COMPONENTS IN PATIENTS WITH OSA AND WITHOUT OSA-A HOSPITAL BASED CROSSSECTIONAL STUDY”

Dissertation submitted to

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The Tamil Nadu Dr. M.G.R. Medical University

Chennai – 600032

Tamil Nadu, India

May 2018

BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"TO INVESTIGATE THE PREVALENCE AND ASSOCIATION OF METABOLIC SYNDROME AND ITS COMPONENTS IN PATIENTS WITH OSA AND WITHOUT OSA-A HOSPITAL BASED CROSSSECTIONAL STUDY"** is the bonafide work done by **Dr. C. SUGANYA** during her M.D (Tuberculosis and Respiratory Diseases) course in the academic years 2016-2019, at the Institute of Thoracic Medicine and Rajiv Gandhi Government General Hospital – Madras Medical College, Chennai. This work has not previously formed the basis for the award of any degree.

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DECLARATION BY THE GUIDE

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INTRODUCTION

The combination of obstructive sleep apnea and metabolic syndrome has been termed as syndrome z.Sleep related breathing disorders and metabolic syndrome are on increasing trend because of epidemic of obesity.[(1)] Beyond their epidemiologic relationship, growing evidence suggests that OSA may be causally related to metabolic syndrome. Its prevalence varies from 74 to 85% among patients with obstructive sleep apnea and from 37 to 41% among patients with nonobstructive sleep apnea.(2)

Metabolic syndrome

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) report[2] defines metabolic syndrome as three or more of the following five variables: hypertension, increased fasting blood glucose, low high-density lipoprotein cholesterol (HDL-C), elevated serum triglyceride, and abdominal obesity. (3)

Obstructive sleep apnea

Obstructive sleep apnea syndrome is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation.(4) Structural factors like increased volume of tongue, lateral pharyngeal wall and soft tissue are significant risk factors for OSA. OSA patients have anatomically small pharyngeal airways.(5).

In patients with OSA during wakefulness there will be increased pharyngeal dilator muscle activity due to long time neuromuscular compensation. That compensation will be reduced during sleep in patients with OSA combined with reduced reflex activity of muscles during sleep causing airway collapse in apneic patients. This can lead to a combination of hypopneas, reduction in airflow associated with a fall in oxygen saturation, or apneas, complete cessation of airflow.(6)

Polysomnographic features of OSA

An apnea has been defined as > 90 percent reduction from baseline in oronasal thermister airflow. Hypopnea has been defined as an event lasting > 10 sec characterized by > 30 percent reduction from baseline in peak nasal inspiratory airflow associated with > 4 percent reduction in arterial s02 from baseline. RERA has been defined as sequence of breaths not meeting citeria for apnea or hypopnea but causing increased respiratory effort or inspiratory flattening leading to arousal. OSA severity is usually determined as follows: AHI 5-15 indicates mild, 15-30 moderate and over 30 severe OSAS. In an urban setting in northern India, the prevalence of obstructive sleep apnea and the obstructive sleep apnea syndrome is reported to be 13.7% and 3.8%, respectively.(7)

Polysomnographic monitoring of obstructive sleep apnea syndrome should consist of monitoring of sleep by electroencephalography, electrooculography, electromyography, airflow, and respiratory muscle effort, and should also include measures of electrocardiographic rhythm and blood oxygen saturation.

Changes in cardiac rhythm, particularly bradytachycardia, frequently occur with the apneic episodes. The arterial oxygen saturation level falls during the apneic episode and rises to baseline levels at the termination of the apneic episode. Due to a 10- to 20-second delay in detection of oxygen saturation by subcutaneous monitoring devices, a dissociation may occur between the respiratory patterns and the oxygen-saturation patterns seen on the polysomnogram. Carbon dioxide values in the blood are usually only transiently elevated, but sustained elevations can be seen in some patients.

The obstructive apneic episodes can lead to gastroesophageal reflux in some patients; reflux can be detected during sleep by intraesophageal pH monitoring. Sleep is disrupted by arousals that usually occur at the termination of the apneic events, resulting in excessive daytime sleepiness, which may be detected by either the multiple sleep latency test (MSLT) or other tests of daytime alertness and sleepiness. Mean sleep latencies on the MSLT are often below 10 minutes and can be below 5 minutes (normal 10 to 20 minutes). Sleep-onset REM periods during the naps are not typical, but sleep-onset REM periods can occur on every nap.(4)

Other Laboratory Test Features

Awake arterial blood gas measurements are usually normal, but some patients with severe obstructive sleep apnea syndrome can show abnormal values. Cephalometric radiographs, magnetic resonance imaging, computed tomographic scanning of the upper airways or fibreoptic endoscopy can show obstruction of the upper airway. Cardiac testing may show evidence of impaired right ventricular function in some patients with severe obstructive sleep apnea syndrome. Hematologic studies may also show an elevated hemoglobin or hematocrit value, indicating polycythemia.(4)

Diagnostic Criteria: Obstructive Sleep Apnea Syndrome

A. The patient has a complaint of excessive sleepiness or insomnia. Occasionally, the patient may be unaware of clinical features that are observed by others.

B. Frequent episodes of obstructed breathing occur during sleep.

C. Associated features include:

1. Loud snoring
2. Morning headaches
3. A dry mouth upon awakening
4. Chest retraction during sleep in young children

D. Polysomnographic monitoring demonstrates:

1. More than five obstructive apneas, greater than 10 seconds in duration, per hour of sleep and one or more of the following:

    a. Frequent arousals from sleep associated with the apneas

    b. Bradytachycardia

    c. Arterial oxygen desaturation in association with the apneic episodes

2. MSLT may or may not demonstrate a mean sleep latency of less than 10 minutes.

E. The symptoms can be associated with other medical disorders (e.g., tonsillar enlargement).

F. Other sleep disorders can be present (e.g., periodic limb movement disorder or narcolepsy

Although metabolic syndrome and OSA may be coincident syndromes, there is growing evidence that the pathophysiology of OSA and metabolic syndrome overlap considerably. We are only beginning to understand the potential mechanisms underlying the OSA–metabolic syndrome interaction. Although there is no clear consensus, there is growing evidence that alterations in the hypothalamic–pituitary axis, generation of reactive oxygen species (ROS) due to repetitive hypoxia, inflammation, and generation of adipokines may be implicated in the changes associated with both OSA and metabolic syndrome. Studies on the prevalence of metabolic syndrome and its association in patients with OSA in hospital based population in India is limited.

Prevalence may differ among the various ethnic groups. Establishing prevalence and its association is essential to guide decision making for patients with sleep disturbances as these patients probably have higher burden of metabolic syndrome and to encourage systemic evaluation for the presence of metabolic abnormalities in OSA and vice versa.

REVIEW OF LITERATURE

Definitions of the metabolic syndrome

The metabolic syndrome is a cluster of abnormalities of metabolism that has been found to be associated with a high risk of cardiovascular mortality, coronary heart disease and stroke greater than that of its individual components [8]. The syndrome itself has been otherwise called by various names, such as the insulin resistance syndrome, deadly quartet, syndrome X, syndrome X plus, among others.

The clear definition is essential to compare the prevalence of the metabolic syndrome both among populations and over time, inspite of racial and ethnic differences. Debate arises when considering definition about giving importance to which components of metabolic abnormalities. Before the initial WHO definition of the metabolic syndrome in 1998, there is no uniformity in defining the prevalence of metabolic syndrome among various races.

WHO report 1999 [9], the European Group for the Study of Insulin Resistance (EGIR), in 1999, and the definition of the Adult Treatment Panel III (ATPIII) also known as National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adult— in 2001 [10] are the 2 major recognized definitions of metabolic syndrome.

The ATPIII definition of the metabolic syndrome 2001 was more suitable for clinical practice. No measurement of insulin resistance was included in ATP 3 definition. As per modified NCEP ATPIII criteria (2005 REVISED definition) metabolic syndrome is defined as three out of five of the following features,.Abdominal Obesity(waist circumference >=90 cm for asian males,>=80 cm in asian females), Hyperglycemia (fasting glucose>=100mg/dl or on treatment),.Hypertriglyceridemia (triglyceride >= 150mg/dl or on treatment),Decreased HDL cholesterol(<40mg/dl(M), <50mg/dl(F), Hypertension.(systolic >= 130mmHg or diastolic >= 85mm Hg)

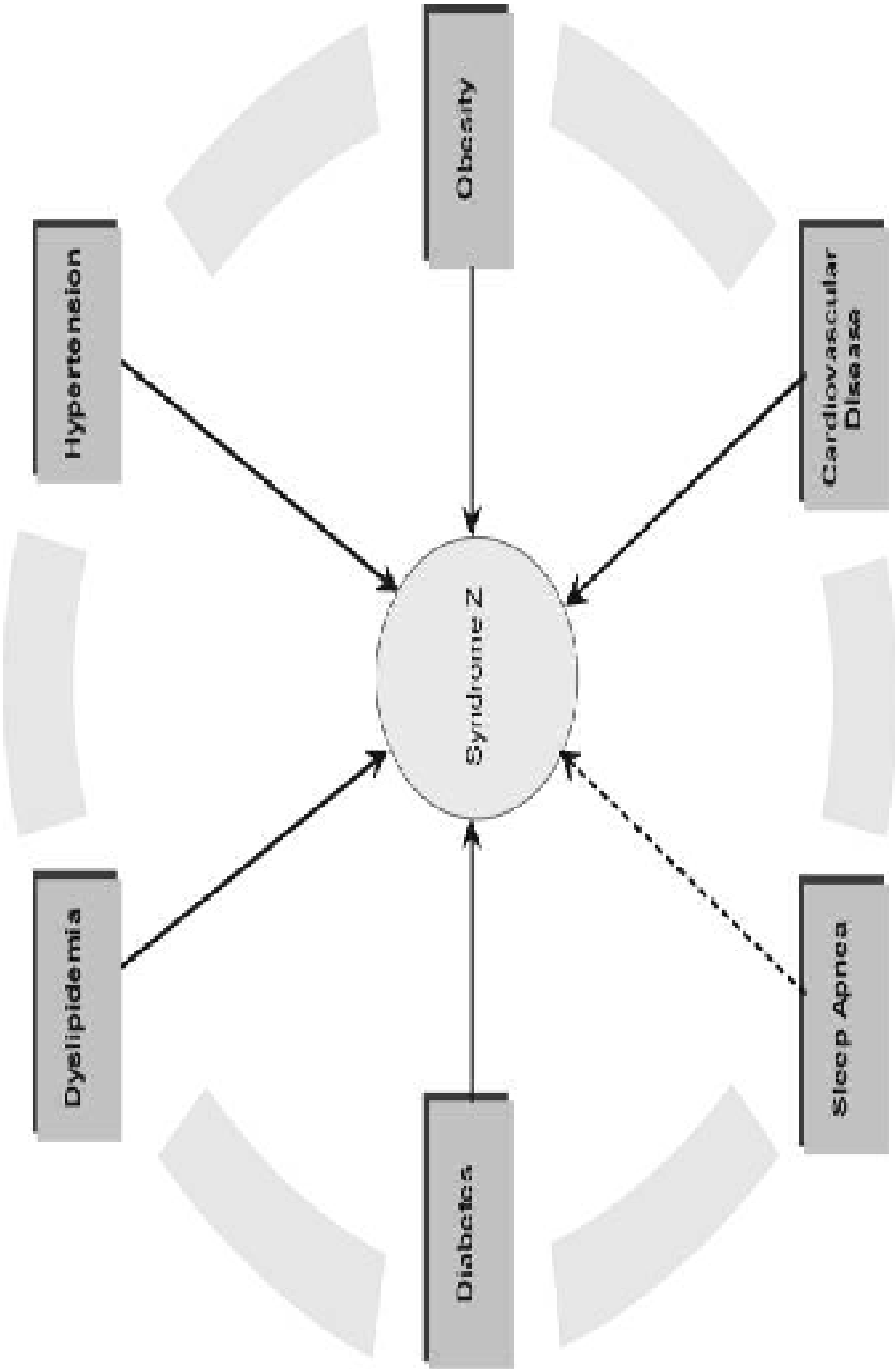

Obesity
Hypertension
Cardiovascular Disease
Syndrome Z
Dyslipidemia
Diabetes
Sleep Apnea

Figure 1

Epidemiology of obstructive sleep apnea

Defining OSA as an AHI ≥5 events/hour in the Wisconsin Sleep Cohort, the prevalence of OSA was 24% in men and 9% in women aged 30-60 years of age (11). The prevalence of OSA with associated excessive daytime somnolence termed as OSAS is approximately 3% to 7% in adult men and 2% to 5% in adult women (12). Prevalence estimates don't vary significantly worldwide suggesting that OSA is as common in the developing world as in western society (13).

OSA and obesity

Obesity, especially central obesity, is one of the strongest risk factors for OSA. Given the worsening modern pandemic of obesity, the prevalence of OSA is on increasing trend. In the Wisconsin Sleep Cohort study, longitudinal analysis over a 4 year period shows 10% increase in body weight confers a 32% increase in AHI and a 6-fold increase in the risk of developing moderate-severe OSA. On the other hand, a 10% decrease in weight was associated with a 26% decrease in the AHI. Changes in other body composition measures (e.g., waist or neck circumference) were not associated with an increase (or decrease) in the AHI after accounting for the changes in weight.(14) Recent data also suggested that modest changes in weight were related to an increase or decrease in SDB, and this association was stronger in men than in women.

In the Sleep Heart Health Study, a multi-centre epidemiologic cohort study of cardiovascular correlates of OSA in middle-aged and older Americans, weight gain of 10 kilograms over a 5-year period conferred a 5.2- and 2.5-fold increase in the likelihood of increasing the AHI by 15 events per hour in men and women respectively(11). The prevalence can be as high as 70% in patients referred for bariatric surgery.(15)

Obesity may alter the normal upper airway mechanics and contribute to the pathophysiology of OSA in a number of ways. Obesity is associated with a reduction in lung volumes, especially functional residual capacity and expiratory reserve volume leading to increased work of breathing.(16) Leptin is a hormone produced by adipocytes and it acts on the central respiratory centres to stimulate ventilation and leptin deficiency or leptin resistance has been associated with hypoventilation.(17) Obesity is characterised by central leptin resistance and there is blunting of the response to hypercapnia. This will lead to worsening of hypercapnia and impairment of arousal from sleep during apneas.(18)

Weight loss should be recommended for all overweight or obese patients with OSA, as it may confer a benefit in reducing OSA severity, Patients with more severe OSA derive more benefit from weight loss than those with milder disease and those who lost most of weight get more benefit.

Bariatric surgeries are also helpful in OSA patients.(19) In a Swedish case-control longitudinal study of more than 3,400 obese patients, the average fall in BMI was -9.7 ± 5 $kg{\cdot}m^{-2}$ compared to 0 ± 3 $kg{\cdot}m^{-2}$ in the control group following bariatric surgery. There was also a marked improvement in OSA symptoms and a lower 2-year incidence of T2DM and hypertriglyceridemia (20). Laparoscopic adjustable gastric banding in a cohort of severely obese patients with moderate to severe OSA resulted in significant weight loss and a decrease in AHI when evaluated at an average of 12 - 24 months after surgery.(21)

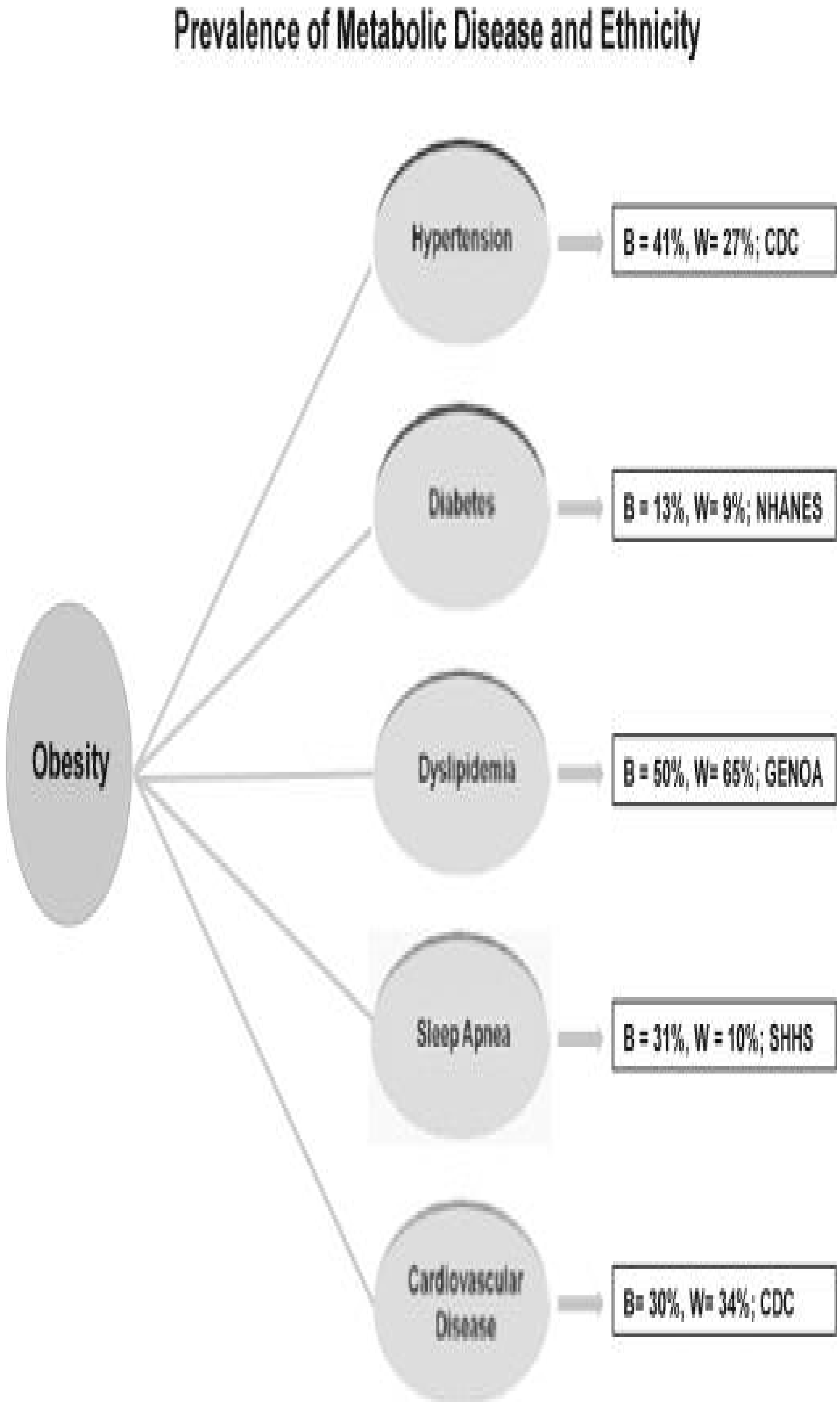

Prevalence of Metabolic Disease and Ethnicity
Obesity
Hypertension
B = 41%, W= 27%; CDC
Diabetes
B = 13%, W= 9%; NHANES
Dyslipidemia
B = 50%, W= 65%; GENOA
Sleep Apnea
B = 31%, W = 10%; SHHS
Cardiovascular Disease
B= 30%, W= 34%; CDC

Figure 2

Prevalence of metabolic diseases linked to obesity based on ethnicity: black (B) vs. white (W). Data were retrieved from the Center for Disease Control (CDC), National Health and Nutrition Examination Survey (NHANES), the Genetic Epidemiology Network of Arteriopathy (GENOA) and the Sleep Heart Health Study (SHHS).

OSA and sex

OSA shows increased prevalence in men with most epidemiological studies showing 2 to 3 fold higher prevalence of OSA in men than women. (22)Sex hormones may also be reason for that. OSA is more prevalent in post-menopausal women than pre-menopausal women, and hormone replacement therapy in post-menopausal women may protect against the disorder.(23)

OSA and age

The Sleep Heart Health Study demonstrated that the prevalence of OSA increases with age and plateau after the age of 60 years, and the cardiovascular mortality and other risk factors associated with OSA is mainly limited to middle-aged adults, especially men(11). Some studies demonstrated that with aging, there is increased deposition of parapharyngeal fat in both sexes; lengthening of the soft palate, significantly in women; and a change in the bony shape surrounding the pharynx. These physiological and anatomical differences could predispose to pharyngeal collapse during sleep (24) Some researchers have suggested that the mortality risk with sleep apnea may even decrease in the elderly because of adaptive responses to chronic intermittent hypoxia.(25)

OSA AND MALLAMPATTI SCORING

Patients with OSA have reduced upper airway cross-sectional area compared to patients without OSA. These anatomical deficits in the upper airway and collapsibility are more likely to be involved in the pathogenesis of OSA. Mallampati classification an anesthetic assessment of difficulty in intubation risk based on the morphology of the oropharynx, will be a possible simple assessment tool for OSA. This simple assessment tool was first described by Mallampati et al in 1985 with only 3 grades, but was later modified to 4 classes as modified Mallampati class.

The assessment is made with the patient sitting with the head in a neutral position, the mouth opened, and the tongue protruded maximally without phonation. The class is then graded based on the visibility of the airway structures

Grade I – tonsils, pillars and soft palate are all clearly visible;

Grade II – the uvula, pillars and upper pole are visible;

Grade III – only part of the soft palate is visible but the uvula is partly obscured, and

Grade IV – only the hard palate is visible.

Figure 3

There may be good inter-observer agreement with the use of this classification, especially in more senior clinicians. There is some validation of the use of Mallampati class in clinical assessment for sleep apnea.

Hiremath et al[26] reported that a higher Mallampati class (more oropharyngeal crowding) was associated with increased prevalence of both OSA and difficult intubation in a cohort of patients undergoing anesthesia. Liistro[27] reported a significant correlation between AHI and Mallampati class in 202 subjects undergoing polysomnography, but this association was only significant in those with nasal obstruction (62% of the cohort). The odds ratio (OR) of an AHI > 15 was 2.45 (95% CI 1.23-4.84) in subjects with nasal obstruction and a Mallampati class III-IV relative to class I-II. There was no increased OR seen in those without nasal obstruction. Yagi et al[28] similarly reported a statistically significant correlation between Modified Mallampati class and AHI in 141 patients.

Morinaga et al[29] from the same institution also reported on the clinical utility of the Modified Mallampati class, but this time assessed the changes in AHI following nasal surgery. This group reported that improvements in AHI were negatively correlated with the Mallampati class, that is, higher degrees of oropharyngeal crowding were associated with lesser changes in AHI after nasal surgery. Nuckton et al[30] prospectively assessed 137 patients attending a sleep clinic and reported an OR for OSA (defined as an AHI $\geq$ 5) of 2.5 (95% confidence interval [CI] 1.2-3.2) for each point increase in Mallampati class. The OR for Mallampati class was higher more than those of witnessed apneas and neck circumference. The authors concluded that the Mallampati class was a useful component of the clinical examination that had clinical value in predicting the presence of severity of OSA.

Ramachandran et al[31] recently reported on Mallampati class as a component of a multi-variate prediction score derived from a large retrospective cohort of patients undergoing surgery and validated prospectively in a sleep clinic population. Although the primary variable was a multi-variate prediction score, this group reported that Mallampati class III or IV was an independent predictor of an AHI $>$ 5 with a hazard ratio of 2.7 (95% CI 2.5-3.0), which is quite similar to the data of Nuckton.

OSA INSULIN RESISTENCE AND DIABETES

OSA has been linked to diabetes mellitus. In a cross-sectional study, up to 23% of a diabetic population were found to have OSA.(32) Einhorn et al, found that 48% of diabetic patients had OSA with AHI ≥ 10/hr.(33) Conversely, there is a high prevalence of DM or insulin resistance in OSA patients. In a large clinic-based cross-sectional study, 30.1% of OSA patients had Type 2 DM, while 20% had impaired glucose tolerance.(34) Meta analysis has found that moderate-to-severe OSA was associated with an increased incidence of Type 2 DM.(35)

One study reported that the number of hypoxic episodes correlated with insulin resistance,[36] with another showing a modest correlation between AHI and fasting insulin, but not fasting blood glucose levels.[37] Some data shows a reduction in insulin resistance in obese patients with OSA and type 2 diabetes treated with CPAP,[38]whereas some found that while CPAP improved hypertension and daytime sleepiness, it will not alter insulin resistance.[39] A systematic review and meta-analysis shows inconsistent results with CPAP treatment and insulin resistance, may be because of poor compliance with CPAP or irreversible changes associated with OSA(40)

OSA AND DYSLIPIDEMIA

Dyslipidemia, is defined as abnormally elevated total cholesterol or triglycerides with or without a corresponding significantly reduced high density lipoprotein (HDL). It is associated with progressive atherosclerosis in susceptible individuals (44) Recently, there is a rejuvenated interest on the role of OSA in the development of metabolic syndrome including dyslipidemia, a surrogate marker for atherosclerosis.

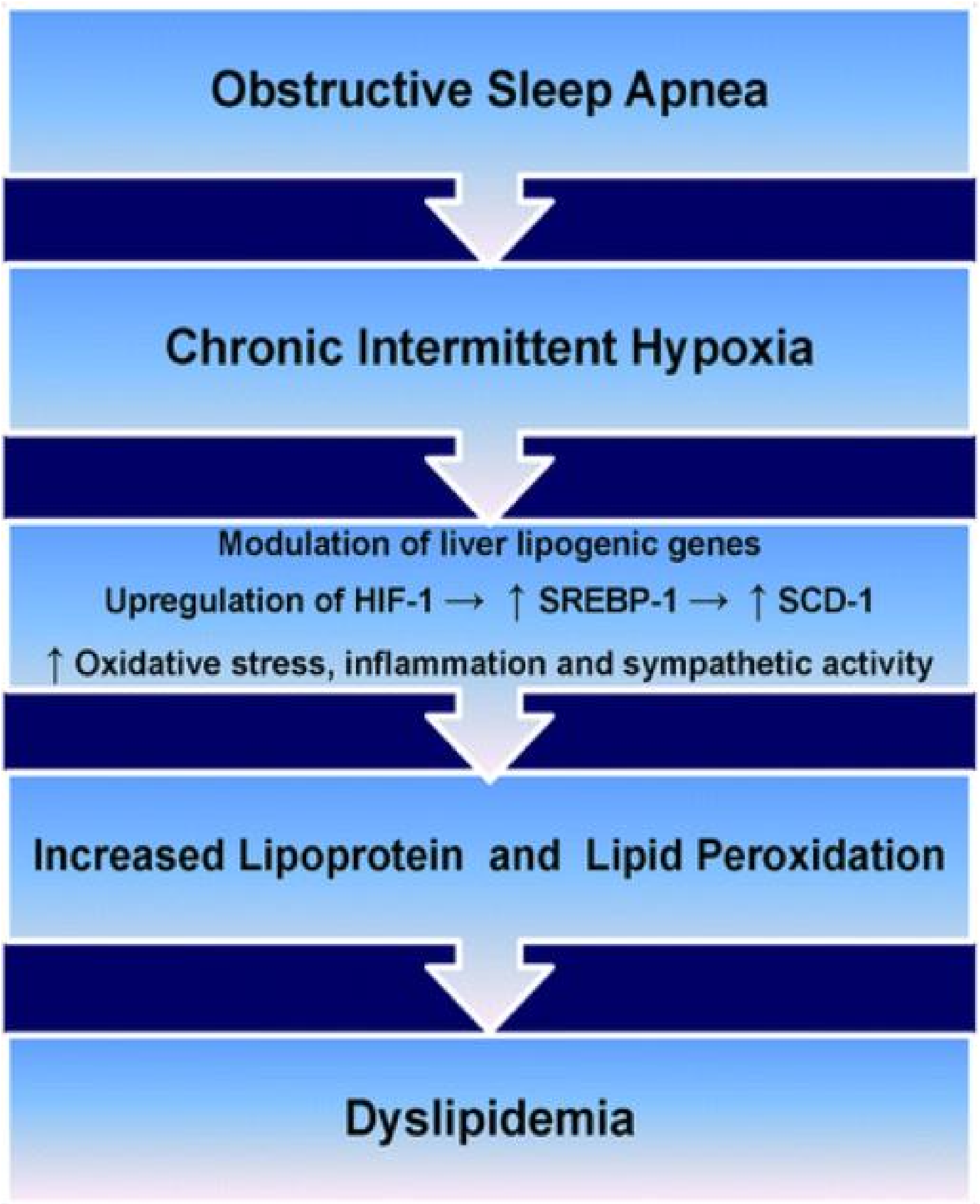


Figure 4

OSA AND HYPERTENSION

In normal individual there will be nocturnal decrease in the blood pressure and this seems to be altered in patients with OSA, Night-time BP may reflect cardiovascular risk as well as day-time BP, and alteration in the night time decrease has been shown to increased cardiovascular adverse events.(43)

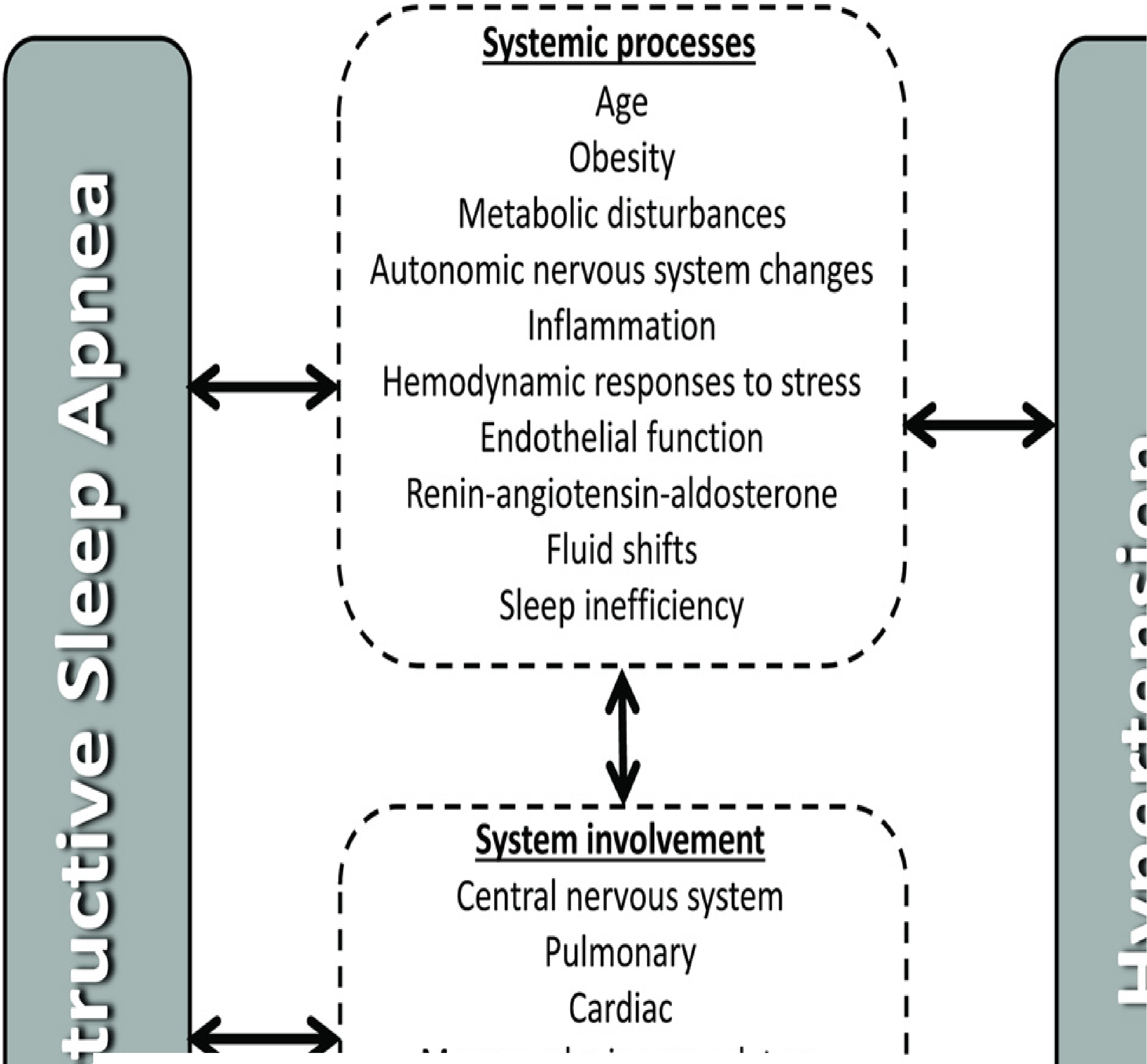


Figure 5

The large prospective Sleep Cohort Study, showed a preventive role of CPAP in reducing new hypertension cases. This study reported a lower incidence of newly diagnosed HTN in those OSA patients who tolerated CPAP. Although long term outcomes is less clear several studies has shown a acute decrease in blood pressure with effective CPAP treatment.(14)

OSA and hypothalamic pituitary adrenal axis

The hypothalamic–pituitary–adrenal (HPA) axis plays an important role in pathogenesis of obesity, and visceral fat distribution.[45] The hypoxemia, brief arousals, and sleep fragmentation in OSA alter normal function of the HPA axis.[45] Sleep deprivation is itself associated with pulsatile cortisol release, increased thyrotropin concentration, and the increased activity of the sympathetic nervous system as measured by heart rate variability and reduced glucose tolerance.(46,47)

A study involving 24 hours cortisol measurement shows that obese non apneic patients has low cortisol secretion and apneic patients has increased secretion and that returned to normal with CPAP therapy.[(48)] Carneiro et al. showed that 24 hour heart rate was more in patients with OSA and no differences in morning or evening cortisol levels between obese patients with and without OSA.. However, those with OSA showed a reduction in heart rate and greater cortisol suppression after dexamethasone, after 3 months of CPAP treatment and the greater dexamethasone suppression correlated with pre-

CPAP AHI.[49] The authors concluded that those with OSA suffer from abnormally high activation of both the sympathetic nervous system and HPA.

OSA and inflammation

Inflammatory component appears to be the part of OSA, although the exact mechanisms remains unclear. Obesity itself appears to be a proinflammatory condition, although the effect of weight reduction on inflammation remains unclear. Snoring produces vibratory trauma and that is associated with tissue injury in the upper airway, which will cause elevated interleukin-8 levels.[(50)] Oxidative stress occurs because of repetetitive hypoxia and reoxygenation in OSA and there will be production of reactive oxygen species. This will activate an inflammatory response among patients with OSA...[(51)] .[52]

ROS has many important signaling properties and trigger inflammatory pathwaysthat may activate multiple proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), inter-leukin-6 (IL-6), and IL-8 1.[53] The proinflammatory transcription factor NF-κB is involved in the transcription of multiple genes involved in inflammation, metabolic syndrome, and atherosclerosis.[54]Repetitive hypoxia and reoxygenation causes increased levels of NF-κB in neutrophils and monocytes[55] that correlate with OSA severity and are reduced with treatment by CPAP.[56]

C-reactive protein (CRP) a biomarker of inflammation is produced in response to IL-6. It is an important marker in both cardiovascular disease and the metabolic syndrome. CRP is 2.8 times higher in patients with metabolic syndrome.(57) pharmacologic reduction of CRP levels will lower cardiovascular risk. CRP is also elevated in obese patients independent of OSA. some studies have established independent association between osa and CRP levels after controlling for body mass index. [(58)] another study comparing CRP levels with different OSA severity matched for age and BMI found no increase in CRP and attributing elevation of CRP to the obesity and not OSA.[(59)]Studies on the effects of treatment are equally conflicting. Some studies shows reduction of CRP with CPAP treatment while some shows no change.

OSA and SLEEP DEPRIVATION

Sleep deprivation is also a key component in OSA. Spiegel et al. showed that acute sleep deprivation in healthy young men will cause reduced serum levels of leptin, increased levels of ghrelin, and increased appetite. Higher glucose levels will be induced by sleep deprivation and alters glucose homeostasis, which will cause high glucose levels, insulin resistance, and risk of diabetes.[60] It is known that CPAP treatment will reduce sleep deprivation among patients with OSA,[61] but it is not known whether reduction in sleep deprivation is the one which will cause the normalization of metabolic parameters after CPAP treatment. Sleep deprivation in and of itself seem to be proinflammatory. Meier-Ewert et al. showed that elevated CRP levels are noted in those with an 88-hour period of sleep deprivation and a 10-day period of sleep restriction to 4 hours per night was[62]. IL 6 levels are also elevated in those with 12-day period of sleep restriction and a trend toward higher CRP levels.

IMPORTANCE OF CONFOUNDING FACTORS

Since cardiovascular disease and obstructive sleep apnea has common risk factors like age, gender, race/ethnicity, and obesity, these could confound the observed associations.[63] Patients with obstructive sleep apnea were generally unhealthy and that also must be taken into account. One study pointed out that risk of 10 year cardiovascular disease was 30 percent among patients with OSA..[64]

Large-scale epidemiologic studies have confirmed that obstructive sleep apnea has been independently associated with cardiovascular disease, with proper statistical control for known confounding factors.[65] In one of studies, risk of stroke or death was increased by obstructive sleep apnea (hazard ratio = 1.97; 95% CI: 1.12– 3.48) independently of other risk factors like age, sex, race, smoking, alcohol consumption, body mass index, atrial fibrillation diabetes mellitus, dyslipidemia,, and hypertension. Another study shows that patients with an apnea hypopnea index (AHI) ≥ 20 had significantly greater odds for stroke than patients without sleep apnea (AHI < 5).[66]

OSA AND SYMPATHETIC NERVOUS SYSTEM ACTIVITY

Studies showed that patients with sleep apnea were characterized by higher levels of sympathetic nervous system activity during wakefulness as well during sleep, relative to healthy controls. [67] During apnea events, oxygen levels will decrease and carbon dioxide levels will increase commensurately, which will activate the sympathetic ner vous system. Higher level of sympathetic nervous system activity induced blood vessel constriction, with blood pressure rising to 250/150 mm Hg. Those patients also exhibited faster heart rates during wakefulness.

Sleep Apnea and Cardiovascular Disease

In the Sleep Heart Health Study with a sample of 6,424 community based population who underwent home polysomnography, shows increased risk of coronary artery disease, congestive heart failure, and stroke among patients with severe obstructive sleep apnea. Specific analysis of the Sleep Heart Health Study shows that individuals with obstructive sleep apnea had 4 times increased risk for atrial fibrillation (adjusted OR = 4.02; 95% CI: 1.03–15.74).[68] The Sleep Heart Health Study also revealed that odds for coronary heart disease (OR = 4.02; 95% CI: 1.03–15.74) and tachycardia (OR = 3.40; 95% CI: 1.03–11.20) were greater among the individuals with obstructive sleep apnea.[69]

The exact underlying mechanism which will explain the underlying association between OSA and cardiovascular disease is not exactly understood several hypothesis have been proposed. These include sustained sympathetic activation,[70] and oxidative stress, with formation of reactive oxygen species which will cause consequently vascular inflammation from the apnea hypoxia and reoxgenation cycles.[71]

Repetitive apneic/hypopneic events along with ensuing arterial desaturation will cause activation of the sympathetic nervous system.[71] This will lead to increases in systolic blood pressure which will lead to hypertension. Bradyarrhythmias are much more common than tachyarrhythmia which might be the resulting effect of an increase in vagal tone because of the stimulation of receptor sites in the upper airway.[72] Disorders in coagulation factors, endothelial damage, platelet activation may also cause increase in inflammatory mediators.[72]Patients with obstructive sleep apnea have greater elevated endothelin levels and that is believed to impair blood pressure regulation as well. Elevated endothelin levels will return To normal with effective CPAP treatment.

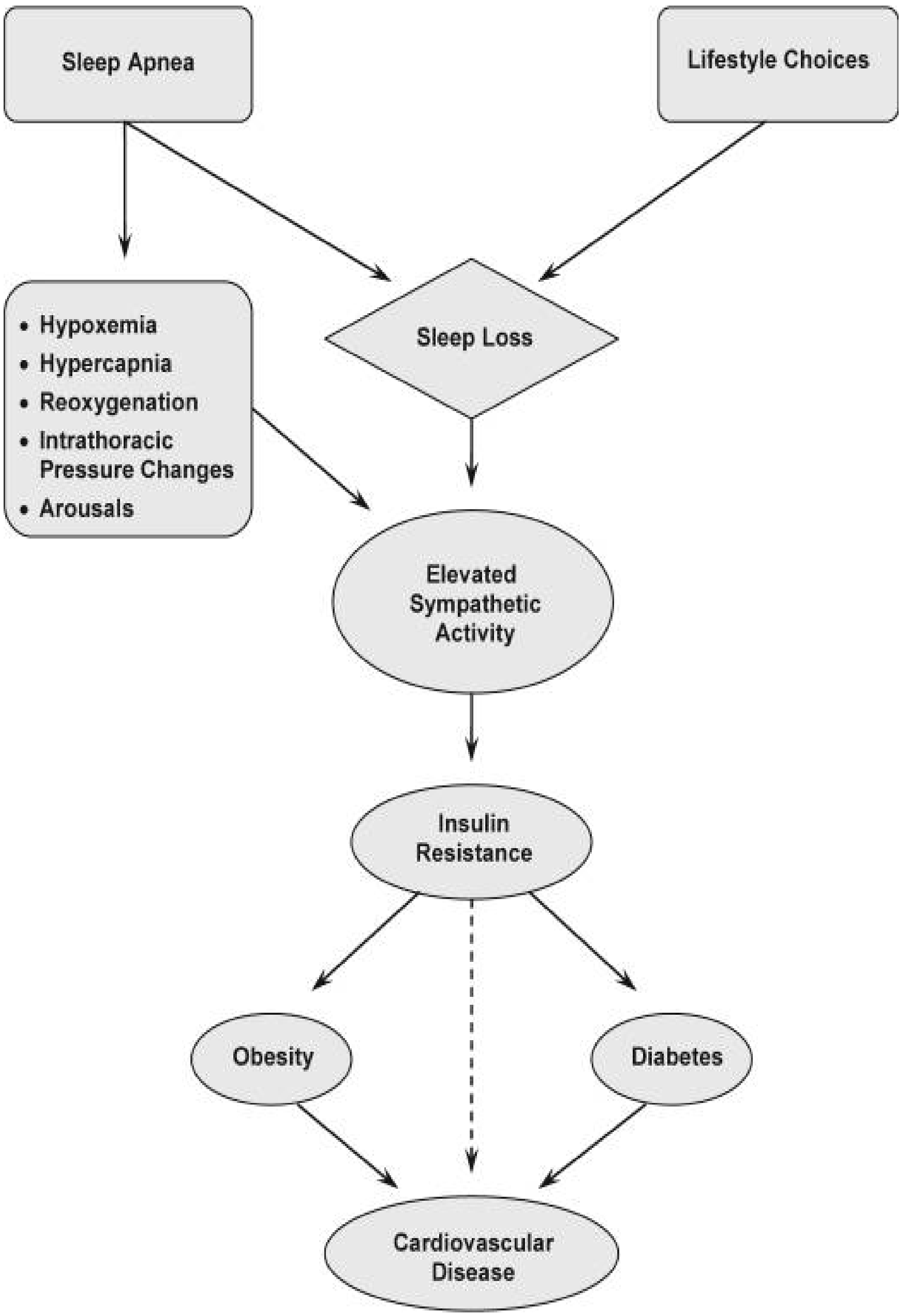

Sleep Apnea
Lifestyle Choices
• Hypoxemia
• Hypercapnia
• Reoxygenation
• Intrathoracic Pressure Changes
• Arousals
Sleep Loss
Elevated Sympathetic Activity
Insulin Resistance
Obesity
Diabetes
Cardiovascular Disease

Figure 6

It is proposed that hypoxia observed in sleep apnea will promotes the formation of reactive oxygen species, during the reoxygenation period which will activate the transcriptional activator hypoxia-inducible factor 1 (HIF-1).[72] It has also been suggested that transcription factors, which elicit inflammatory pathways are also activated, which will affect inflammatory and immune responses by promoting activation of platelets endothelial cells and leukocytes..[70] Proinflammatory cytokines released will cause endothelial injury and dysfunction leading to cardiovascular morbidity.

This chain of events, occurring during obstructive sleep apnea will provoke atherogenic insult.[71.] These insults occurs before onset of disease since symptoms usually starts after 45 years.[71] Some atherogenic processes are permanent but CPAP treatment will reduce progression.[72] Using CPAP therapy, there is significant reductions in levels of C-reactive protein and interleukin-6,[72] so sleep disorder to be diagnosed as early as possible to retard the progression of disease. Some studies shows positive results, like reduced systolic blood pressure, improves left ventricular systolic function, and increased ejection fraction on patients on CPAP therapy of patients with OSA and heart failure.

The relationships between obstructive sleep apnea and cardiovascular disease are rather complex. Several systematic studies are necessary to look for these relationships.

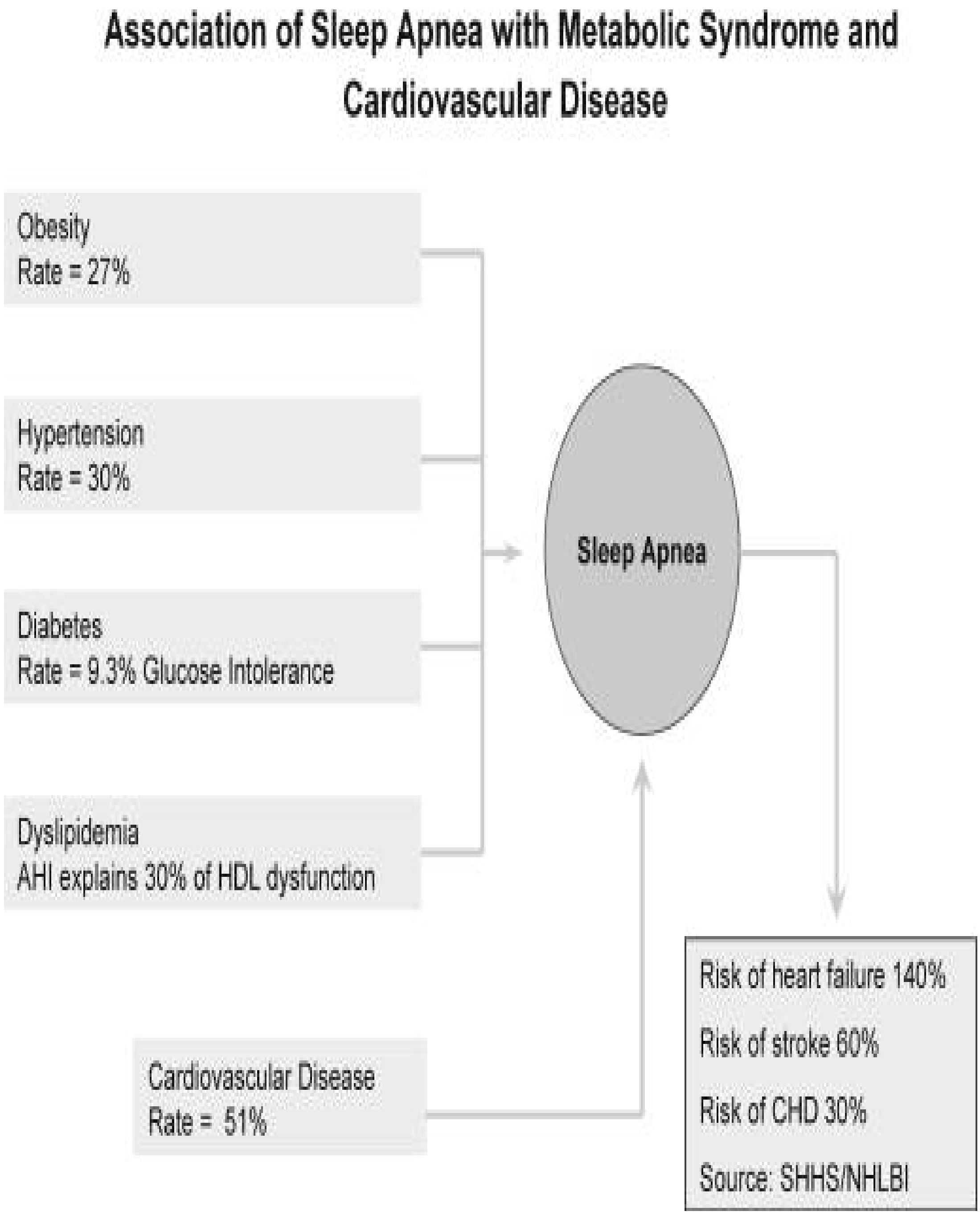

Association of Sleep Apnea with Metabolic Syndrome and Cardiovascular Disease
Obesity
Rate = 27%
Hypertension
Rate = 30%
Diabetes
Rate = 9.3% Glucose Intolerance
Dyslipidemia
AHI explains 30% of HDL dysfunction
Sleep Apnea
Cardiovascular Disease
Rate = 51%
Risk of heart failure 140%
Risk of stroke 60%
Risk of CHD 30%
Source: SHHS/NHLBI

Figure 7

POTENTIAL BENEFITS OF SLEEP APNEA TREATMENT

Clinical trials involving the use of CPAP or bilevel PAP therapy have shown positive results. CPAP treatment is very effective in improving quality of life and left ventricular ejection fraction and, lowers blood pressure and sympathetic activity, and reduces mortality among patients with congestive heart failure.(14)

Among patients with coronary artery disease, CPAP treatment significantly reduces risks of acute coronary syndrome, cardiovascular death and hospitalization for heart failure. Moreover, CPAP therapy has significant effects on lipid levels. CPAP studies show significant improvement in left ventricular function and insulin sensitivity and with a corresponding decrease in blood pressure.(14)

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) identifies the metabolic syndrome as a important target of risk-reduction therapy. It is recommended by them that patients meeting criteria for the syndrome receive adequate treatment aimed at reducing obesity through lifestyle modifications like increased physical activity and improved dietary habits.

Evidence suggests that weight loss among overweight and obese individuals reduces blood pressure, and improves blood glucose levels and improves lipid profiles. Behavioural therapy is first option and Pharmacotherapy is recommended only for those individuals who do not respond positively to behavioral therapies. As gradual sleep loss in the population may be because of sequaelae of sleep apnea or behaviorally determined it is a strong determinant of insulin resistance and individuals at risk for developing cardiovascular disease should be encouraged not to decrease their sleep time.

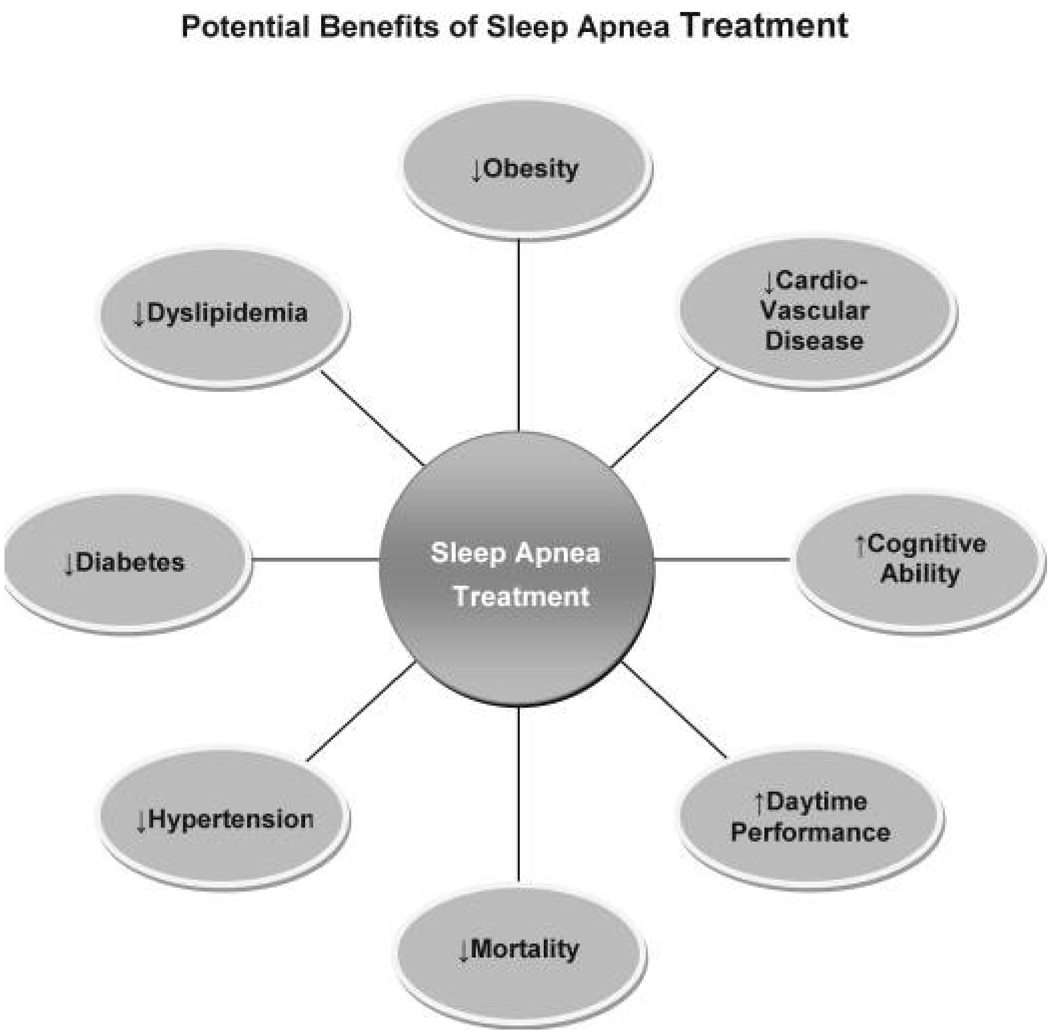


Figure 8

AIM AND OBJECTIVE

PRIMARY OBJECTIVE

To estimate the prevalence of metabolic syndrome in patients with and without OSA in a hospital based population of tertiary healthcare centre in South India.

SECONDARY OBJECTIVE

To investigate the association of metabolic syndrome and its components in patients with and without OSA.

To assess anthropometric indices as an indicator of apnea hypopnea index severity.

MATERIALS AND METHODS

DEFINITION

METABOLIC SYNDROME

As per modified NCEP ATPIII criteria (2005 REVISED definition) metabolic syndrome is defined as three out of five of the following features,

1. Abdominal Obesity (waist circumference >=90 cm for asian males,>=80 cm in asian females),
2. Hyperglycemia (fasting glucose>=100mg/dl or on treatment)
3. Hypertriglyceridemia (triglyceride >= 150mg/dl or on treatment)
4. Decreased HDL cholesterol (<40mg/dl(M), <50mg/dl(F))
5. Hypertension. (systolic >= 130mmHg or diastolic >= 85mm Hg)

OBSTRUCTIVE SLEEP APNEA

OSA was defined as apnoea hypopnea index>5 events/h. Severity of OSA was graded as

mild OSA >=5 <15 events/hr

moderate OSA >=15 <30 events/hr

severe OSA AHI>=30 events/hr

STUDY DESIGN

It is a prospective cross sectional observational study to estimate prevalence of metabolic syndrome in patients with obstructive sleep apnea.

TIME PERIOD

April 2017 to April 2018

STUDY CENTRE

Rajiv Gandhi Government General Hospital

STUDY POPULATION

Patients attending OPD of department of thoracic medicine in Rajiv Gandhi Government General Hospital with excessive day time sleepiness and sleep disturbances

SAMPLING METHOD

Consecutive sampling

Sample size calculation:

To test the difference of 30% prevalence of metabolic syndrome between the subjects with OSA and without OSA groups at 5% level of significance and 80% power we need sample size of 36 in each group (36 subjects with OSA and 36 subjects without OSA).

Calculation:

$$n = \frac{\left(Z_{1-\alpha/2}+Z_{1-\beta}\right)^2 [p_1(1-p_1)+p_2(1-p_2)]}{(p_1-p_2)^2}$$

Standard normal value for 5% level of significance = $Z_{1-\alpha/2}$ =1.96

Standard normal value for 80% power, $Z_{1-\beta}$ =0.84

$$n = \frac{(1.96+0.84)^2[0.80(1-0.20)+0.50(1-0.50)]}{(0.80-0.50)^2} = 36$$

ETHICAL CLEARANCE: APPLIED

CONSENT

Informed written consent will be obtained from all patients.

SAMPLE SELECTION

INCLUSION CRITERIA

- Willing for informed written consent
- Males and females aged 30-65 yrs
- Attending thoracic medicine outpatient department with sleep disturbances

EXCLUSION CRITERIA

- Not willing for informed written consent for the study
- Patients having chronic renal failure,

- chronic liver disease,
- facial anamolies
- hypothyroidism
- on harmone replacement therapy or steroids

STUDY PROTOCOL

Patients attending the thoracic medicine OPD with complaints of sleep disturbances will be selected for the study as per inclusion/exclusion criteria and informed written consent will be obtained.

- A detailed history,
- **Presenting history**:

  Chief complaints, ho snoring excessive daytime sleepiness
- **Past history**
- **Treatment history**

  H/O drug intake for any disease
- **Personal history**

  Smoking history, alcoholism, occupation
- **FAMILY HISTORY**

  Diabetes hypertension cardiovascular disorders

- **Comorbidities**

DM/SHT/CAD/COPD/BA/Neurological diseases will be obtained.

- **clinical examination**

All the patients will undergo clinical examination of all the systems. Facial anamolies will be ruled out

Anthropometric Measurements

All measurements were made with standard techniques. weight by digital scales (to within 100 g, without heavy clothing)height barefoot by stadiometer, waist circumference was measured mid-way between the lowest rib and the iliac crest with the subject standing at the end of gentle expiration.

Body mass index

The body mass index of the study population was calculated using the quetlet index.

Body mass index= weight in kg/height in m2

Neck circumference

Neck circumference was measured in the midway of the neck, between mid-cervical spine and mid anterior neck, to within 1 mm, with non-stretchable plastic tape with the subjects standing upright. In men with a laryngeal prominence (Adam's apple), it was measured just below the prominence.

Epsworth sleepiness scale

It is an eight-item, self administered questionnaire, with a total score ranging between 0 and 24. A score of greater than 10 indicates subjective excessive day time sleepiness.

Epworth Sleepiness Scale

Name: ____________________ Today's date: ____________

Your age (Yrs): __________ Your sex (Male = M, Female = F): ______

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

Modified Mallampati Scoring

MMC assessment was performed with the patient sitting upright with his or her mouth maximally opened and tongue protruded without phonation. The participants were assigned to four classes

Class I: Soft palate, fauces, pillars, and uvula are visible.

Class II: Soft palate, fauces, and uvula are visible.

Class III: Soft palate and base of uvula are visible.

Class IV: Soft palate is not visible at all.

Blood pressure

Blood pressure will be measured for all the patients by digital sphygmomanometer with the patient in sitting position in the right arm

Polysomnography assessment

Polysomnography was conducted on the sleep lab of department of thoracic medicine madras medical college. The following parameters were monitored: frontal, central and occipital EEG, electrooculogram (EOG), submentalis EMG, nasal and oral airflow, anterior tibialis EMG, body position and electrocardiogram. Additionally, thoracic and abdominal movements were recorded by inductance plethysmography. Oxygen saturation (SpO_2) was monitored using a pulse oximeter. The tracing was scored using 30 second epochs. After the overnight fasting blood samples will be taken for fasting blood glucose lipid profile (total cholestrol, HDL,LDL)

ANALYSIS PLAN:

All analysis will be performed with SPSS version 14.0 and $p<0.05$ will be considered significant.

RESULTS

PATIENT CHARACTERISTICS

A total of 108 patients attending thoracic medicine outpatient department with sleep disturbances were included in the study after satisfying the inclusion and exclusion criteria

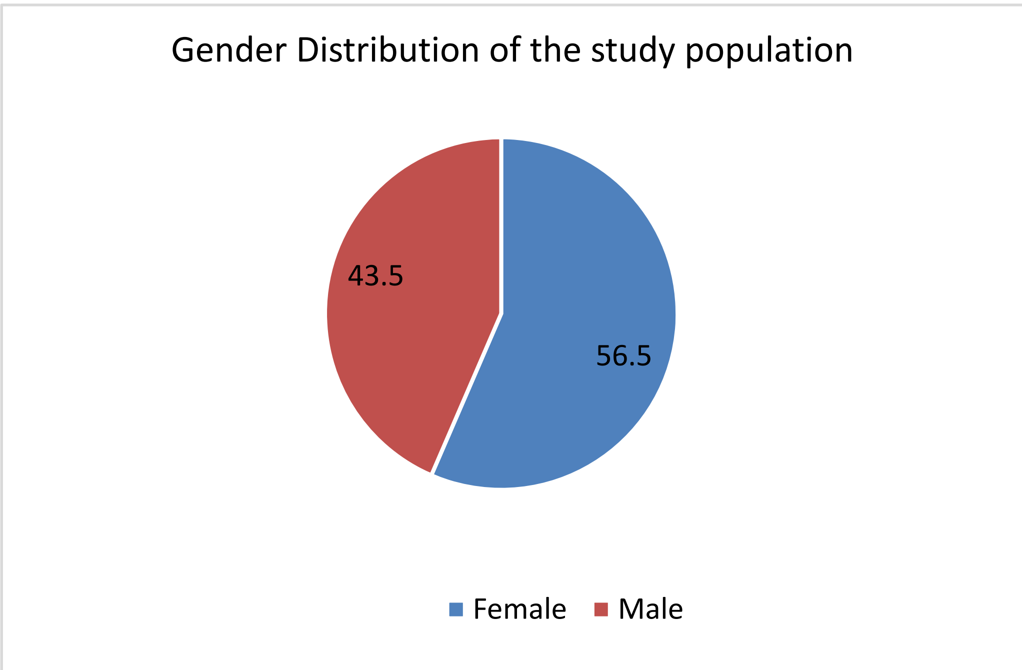
GENDER DISTRIBUTION OF STUDY POPULATION

Out of the 108 patients included in the study 47 were females and 61 were males.

TABLE 1

	Frequency	Percentage (%)
Male	61	56.5
Female	47	43.5
total	108	100

Figure 9



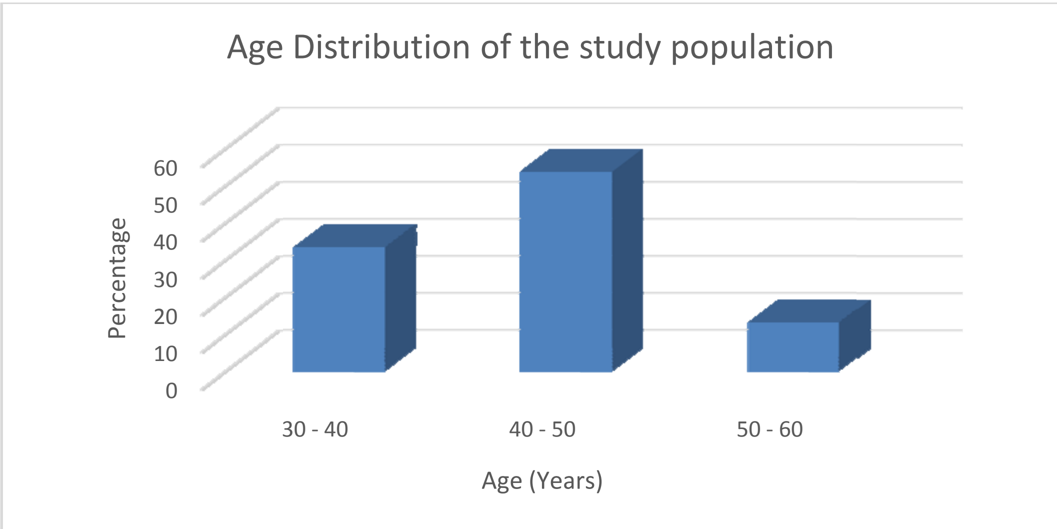
AGE DISTRIBUTION

The number of patients in the age group of 30-40, 40-50, 50-60 were 33.3, 53.7 and 13 percent respectively.

TABLE 2

Age range	Frequency	Percentage (%)
30 - 40	36	33.3
40 - 50	58	53.7
50 - 60	14	13.0

Figure 10



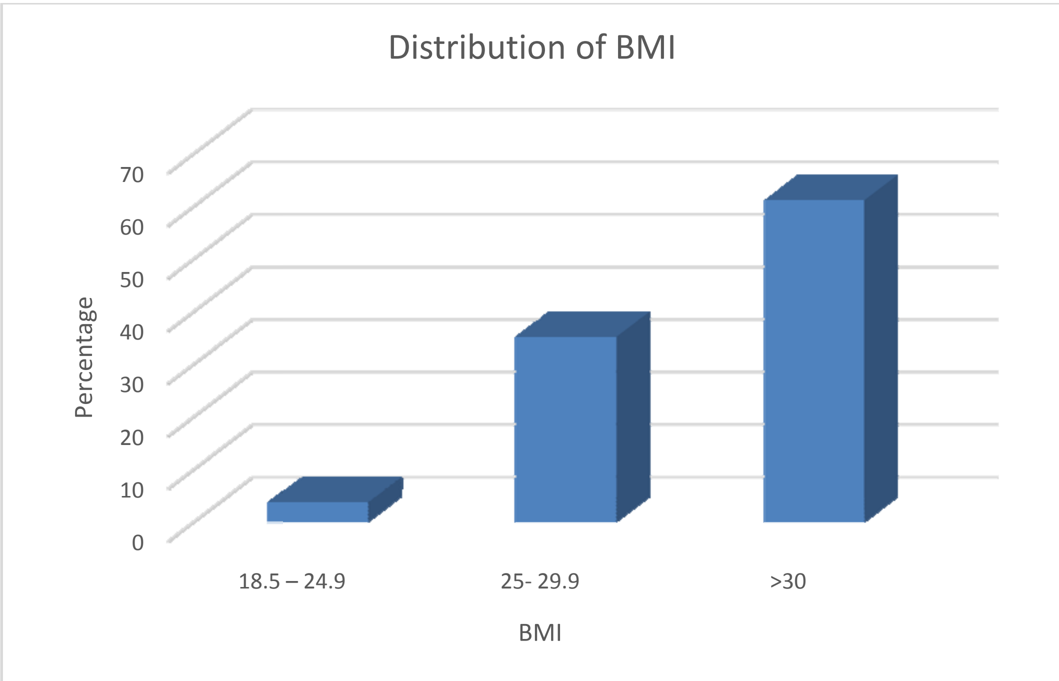
BMI DISTRIBUTION

The body mass index of the study population was calculated by measuring the height, weight and using the quetlet index. Around 61.1 percent has BMI more than 30. 35.2 percent has BMI in the range of 25- 29.9. 3.7 percent has BMI in the range of 18.5 -24.9.

TABLE 3

BMI Group	Frequency	Percentage (%)
18.5 – 24.9	4	3.7
25- 29.9	38	35.2
>30	66	61.1

Figure 11



DESCRIPTIVE STATISTICS OF STUDY POPULATION BASED ON GENDER

TABLE 4

CHARACTERISTICS	**MALE (n=61) mean(SD)**	**Female(n=47) mean(SD)**
AGE	43..4(6.93)	45.3(5.89)
BMI	29.7(2.44)	31.3(4.38)
ABDOMINAL CIRCUMFERENCE	104.7(11.23)	111.3(12.85)
NECK CIRCUMFERENCE	39.9(4.99)	38(3.92)
ESS	13.1(6.80)	12.4(6.47)
LOWEST SO2	85.1(16.16)	85(17.91)

AGE

Mean age of both males and females was around 44.

BMI

Mean BMI for males is 29.7 and for females is 31.3.

ABDOMINAL CIRCUMFERENCE

Abdominal circumference of females was slightly greater than that of males. For males mean abdominal circumference was 104.7 and females it was 111.3

Neck circumference

Neck circumference was almost 38 for both males and females

EPSWORTH SLEEPINESS SCORE

ESS was around 13.1 for males and 12.4 for females TABLE 5

Descriptive statistics of clinical and laboratory findings in study group

TABLE 5

	With OSA (n = 69)	**WITHOUT OSA (n = 39)**
AGE[a]	44.6 (7.0)	43.6 (5.7)
SEX (Female)[c]	30 (43.5)	17 (43.6)
NECK CIRCUMFERENCE [b]	41 (7)	35 (2)
ABDOMINAL CIRUMFERENCE [b]	114 (22)	98 (11)
BMI [b]	31.1 (3.7)	29.0 (2.5)
ESS [b]	16 (6.5)	6 (4)
SBP [b]	130 (20)	124 (15)
DBP [b]	90 (10)	80 (14)
TRIGLYCERIDE [b]	160 (38.5)	160 (30)
HDL [b]	38 (7)	50 (13)
FBS [b]	106 (27)	96 (35)

[a] Mean (SD) for normally distributed data

[b] Median (IQR) for skewed data

[c] n (%) for categorical data

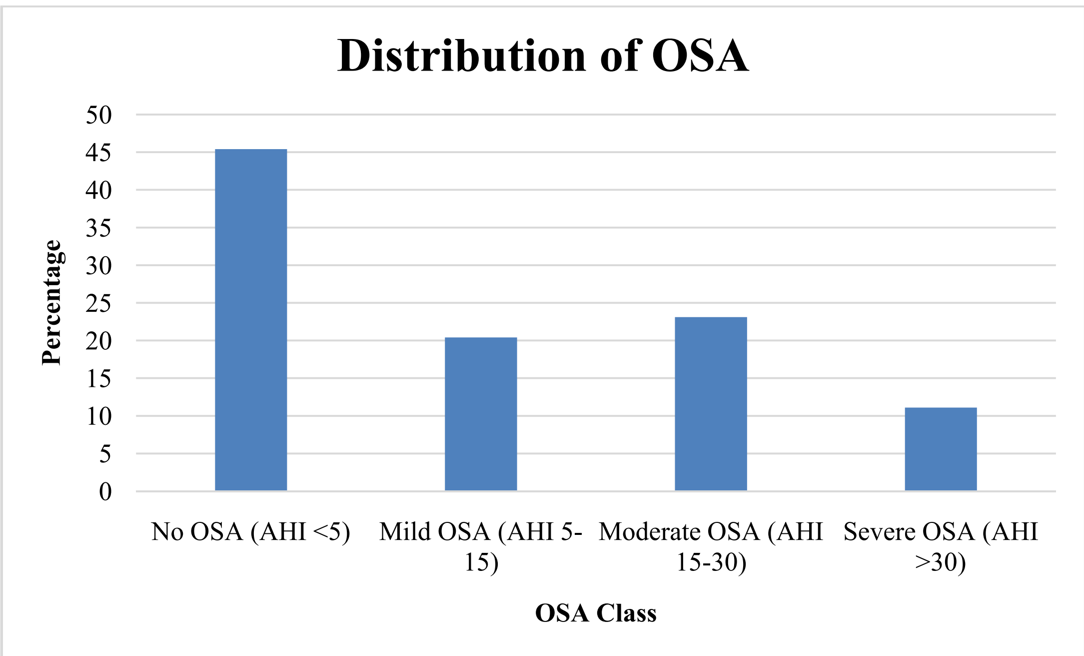
Distribution of mild moderate severe osa among study group

Of the 108 patients who have undergone polysomnography around 49 patients have no OSA and 59 patients have OSA. Of the 59 patients around 22 patients have AHI in the range 5-15 and 25 patients have AHI in range of 15-30 and 12 patients have AHI more than 30.

TABLE 6

	Frequency (n=108)	Percentage (%)
No OSA (AHI <5)	49	45.4
Mild OSA (AHI 5-15)	22	20.4
Moderate OSA (AHI 15-30)	25	23.1
Severe OSA (AHI >30)	12	11.1

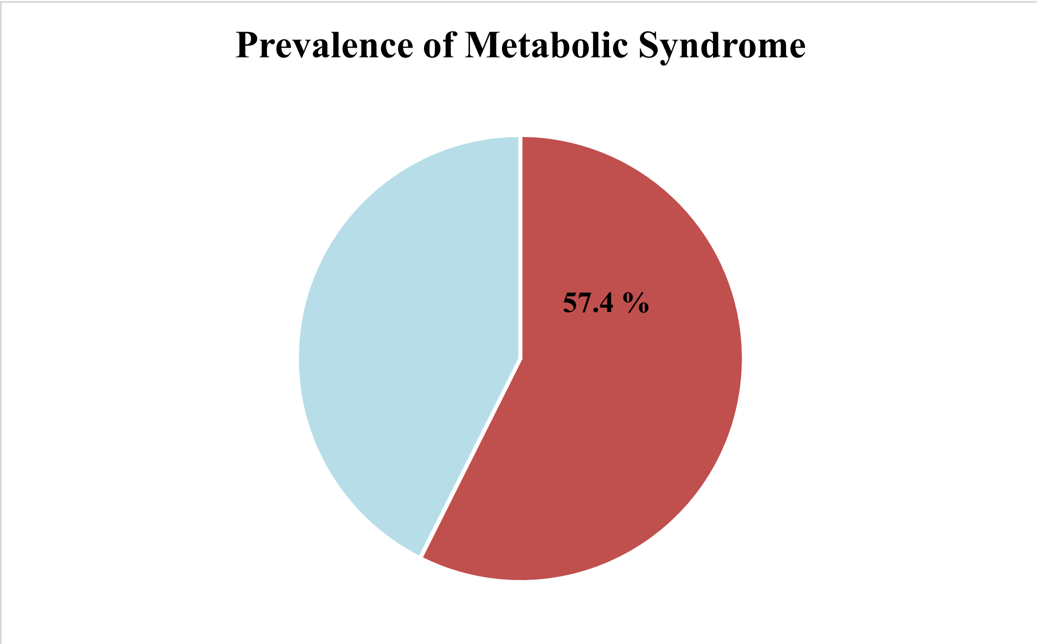
Figure 12



Prevalence of metabolic syndrome among study group

Of the 59 patients with OSA around 57.4 percent has metabolic syndrome.

Figure 13



Prevalence of Metabolic Syndrome Among Study Groups

TABLE 7

	Metabolic Syndrome		p-value[a]
	Present n	**Absent n**	
No OSA (AHI <5)	17(34.7)	32 (65.3)	0.001
Mild OSA (AHI 5-15)	11(50)	11(50)	
Moderate OSA (AHI 15-30)	22 (88)	3 (12)	
Severe OSA (AHI >30)	12 (100)	0	

[a]Chi-square test was used to test the proportional difference between the different groups. The p-value of 0.001 which is less than the 0.05 level of significance implies that there is significant association among OSA status and Metabolic syndrome.

Prevalence of metabolic syndrome among patients without OSA was 34.7 percent. Among the mild OSA patients prevalence was 50 percent 88 percent in moderate OSA group and 100 percent in severe OSA group. Chi square test shows a significant association with a p value of less than 0.001

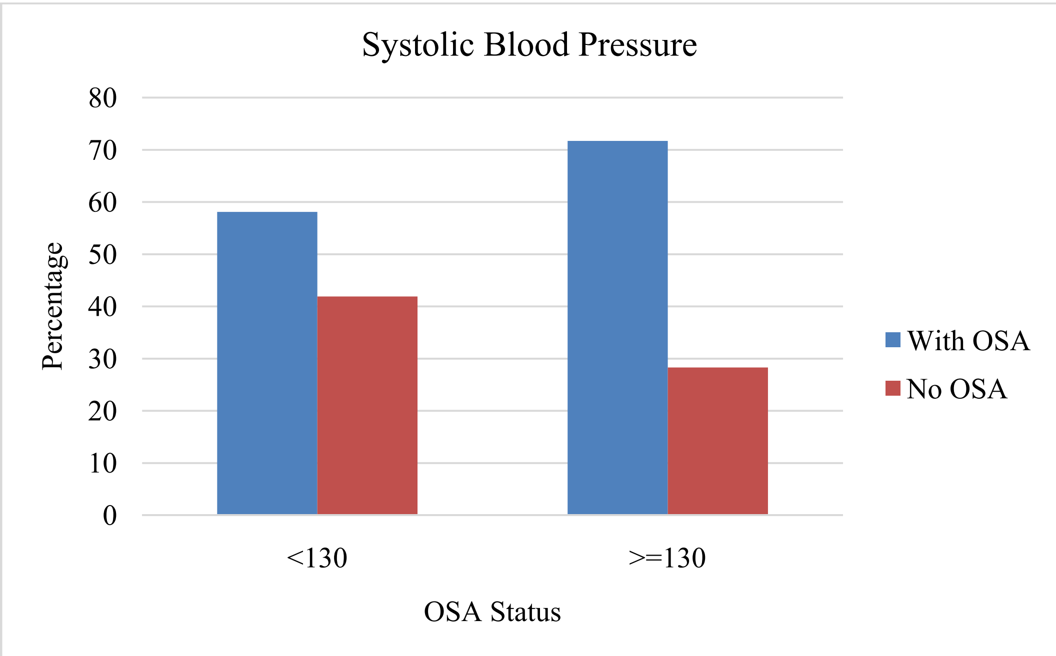
SYSTOLIC BP AMONG STUDY GROUPS

TABLE 8

SYSTOLIC BP	WITH OSA	WITHOUT OSA	p-value[a]
<130	36 (58.1)	26 (41.9)	0.143
>=130	33 (71.7)	12 (28.3)	

[a] Chi-square test was used to test the proportional difference between the different groups. The p-value of 0.143 which is greater than the 0.05 level of significance signifies that there is no significant association among OSA status and systolic blood pressure.

Figure 14



DIASTOLIC BP AMONG STUDY GROUPS

TABLE 9

DIASTOLIC BP	WITH OSA	WITHOUT OSA	p-value[a]
<85	25 (49)	26 (51)	0.002
>85	44 (77.2)	12 (22.8)	

[a] Chi-square test was used to test the proportional difference between the groups. Since, the p-value of the test is less than the 0.05 level of significance, it can be concluded that there is a significant association among OSA status and diastolic blood pressure.

Figure 15

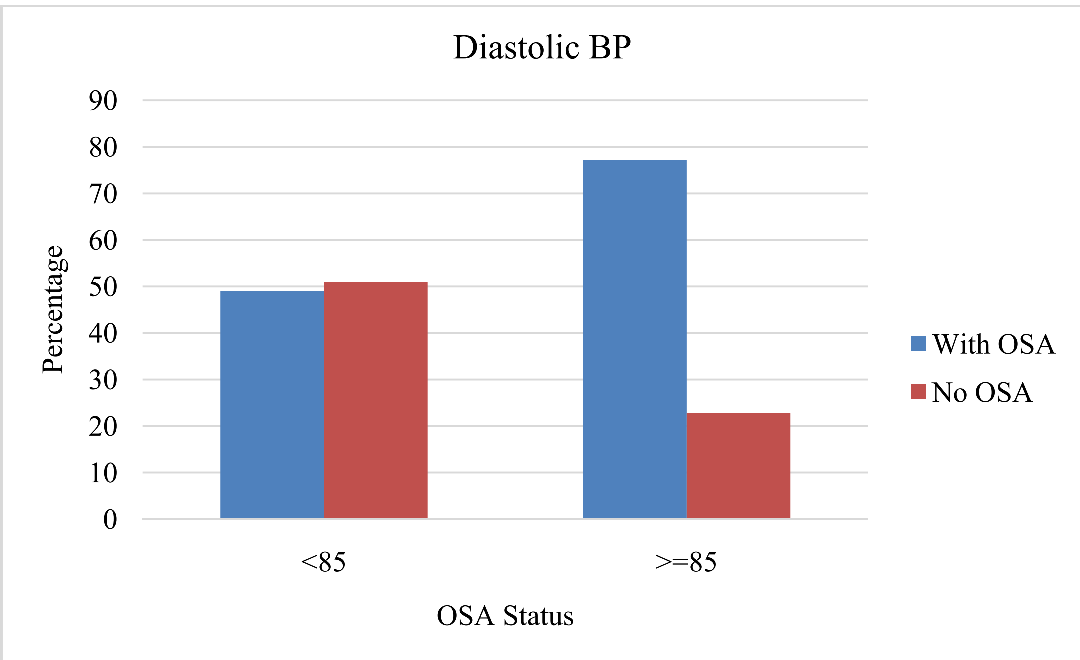


TABLE 10

FBS AMONG STUDY GROUPS

FBS	WITH OSA	WITHOUT OSA	p-value[a]
>100	30 (60)	20 (40)	0.435
<100	39 (67.2)	19 (32.8)	

[a]Chi-square test was used to test the proportional difference between the different groups. From the above the above table, it is concluded that there is no significant association among the OSA status and FBS as the p-value of the test is greater than the 0.05 level of significance.

Figure 16

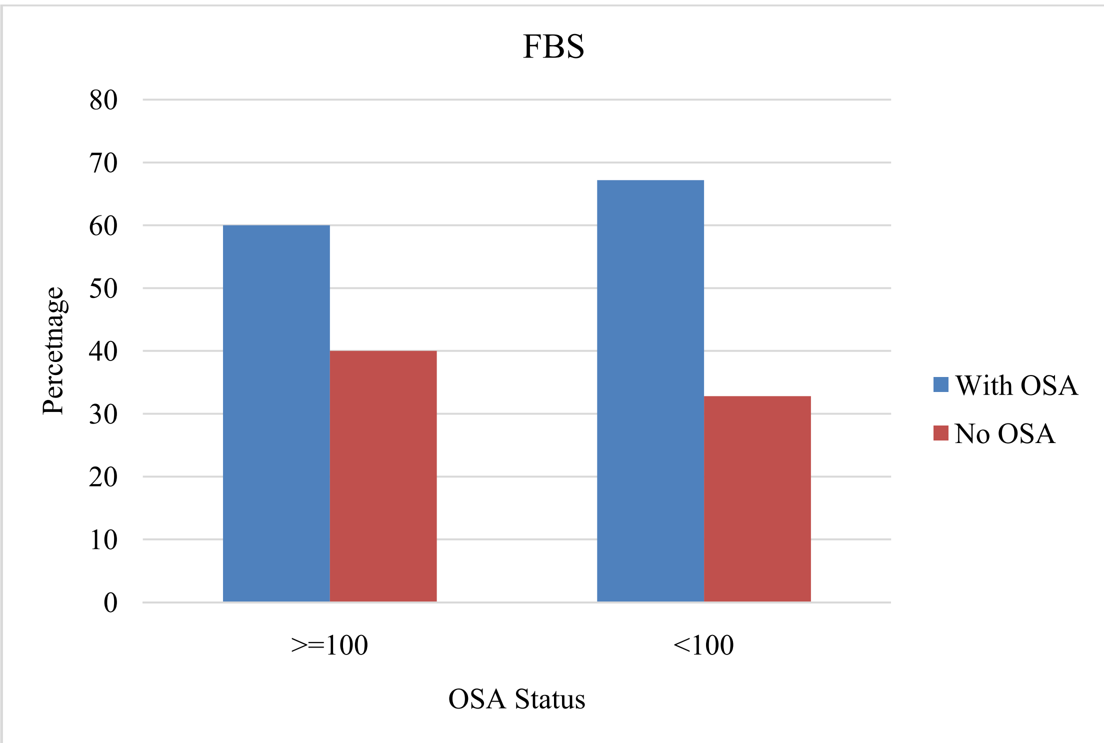


TABLE 11

Abdominal Circumference AMONG STUDY GROUP

HDL	WITH OSA	WITHOUT OSA	p-value[a]
>90 FOR MALES >80 FOR FEMALES	69 (65.1)	37 (34.9)	0.058
<90 FOR MALES <80 FOR FEMALES	0	2 (100)	

[a] Chi-square test was used to test the proportional difference between the different groups. p-value of 0.058 which is greater than the 0.05 level of signifies indicates that there is no significant association between Abdominal Circumference and the OSA Status.

Figure 17

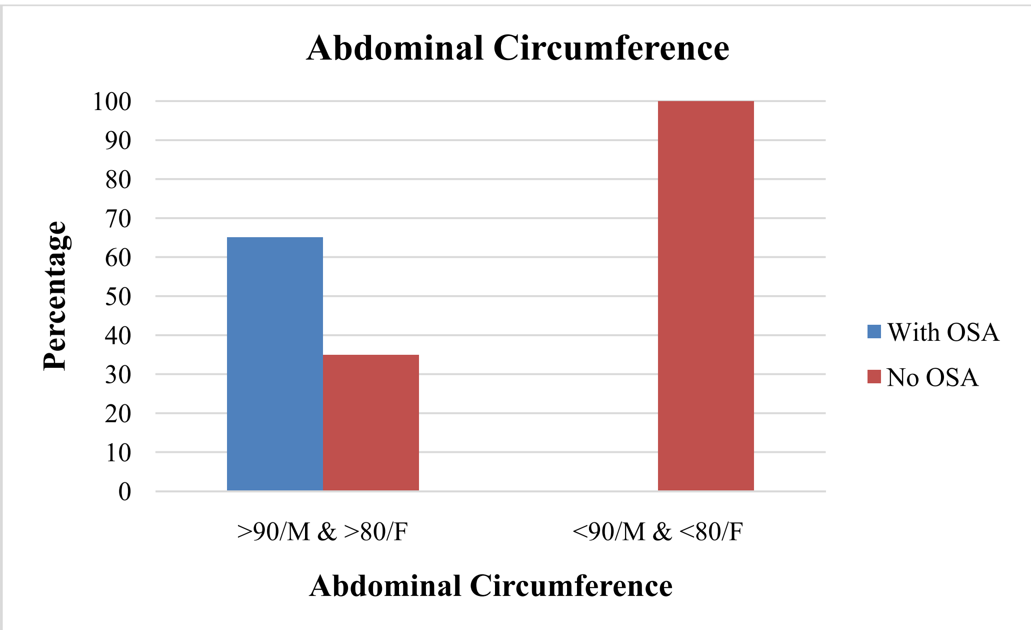


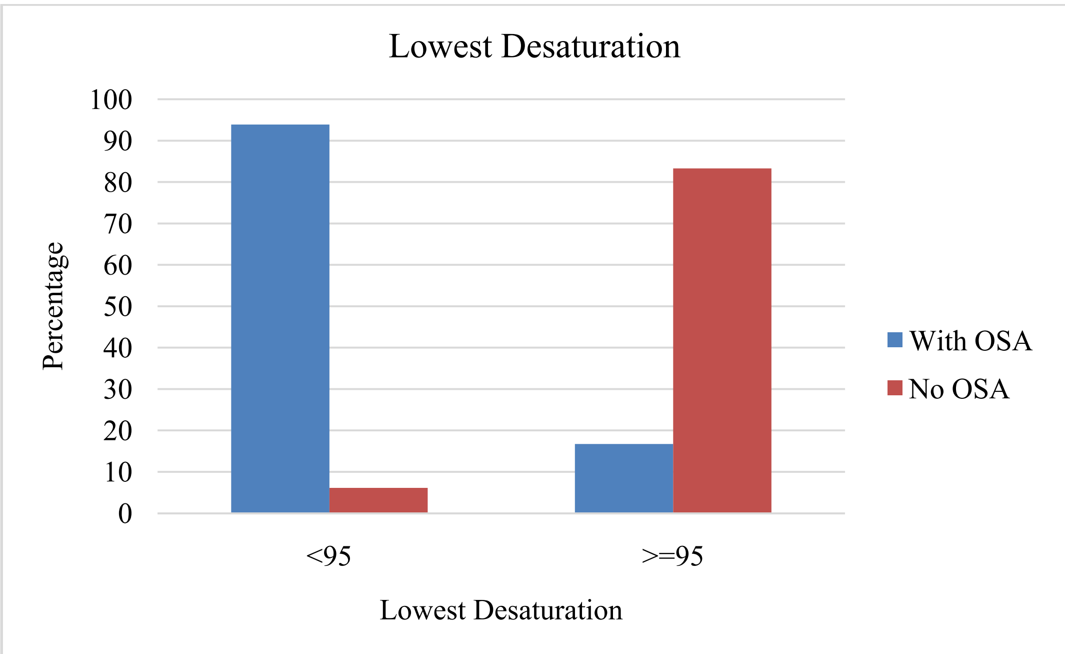
TABLE 12

Lowest desaturation among study groups

	With OSA	**Without OSA**	**p-value[a]**
<95	62 (93.9)	4 (6.1)	<0.001
>95	7 (16.7)	35 (83.3)	

[a] Chi-square test was used to test the proportional difference between the different groups. p-value of <0.001 which is less than the 0.05 level of signifies indicates that there is a significant association between lowest desaturation and the OSA Status.

Figure 18



Mallampati grading among study group

TABLE 13

	With OSA	Without OSA	p-value[a]
Grade 1 and 2	19 (38)	31 (62)	<0.001
Grade 3 and 4	50 (86.2)	8 (13.8)	

[a] Chi-square test was used to test the proportional difference between the different groups. p-value of <0.001 which is less than the 0.05 level of signifies indicates that there is a significant association between mallampati grading and the OSA Status.

Figure 19

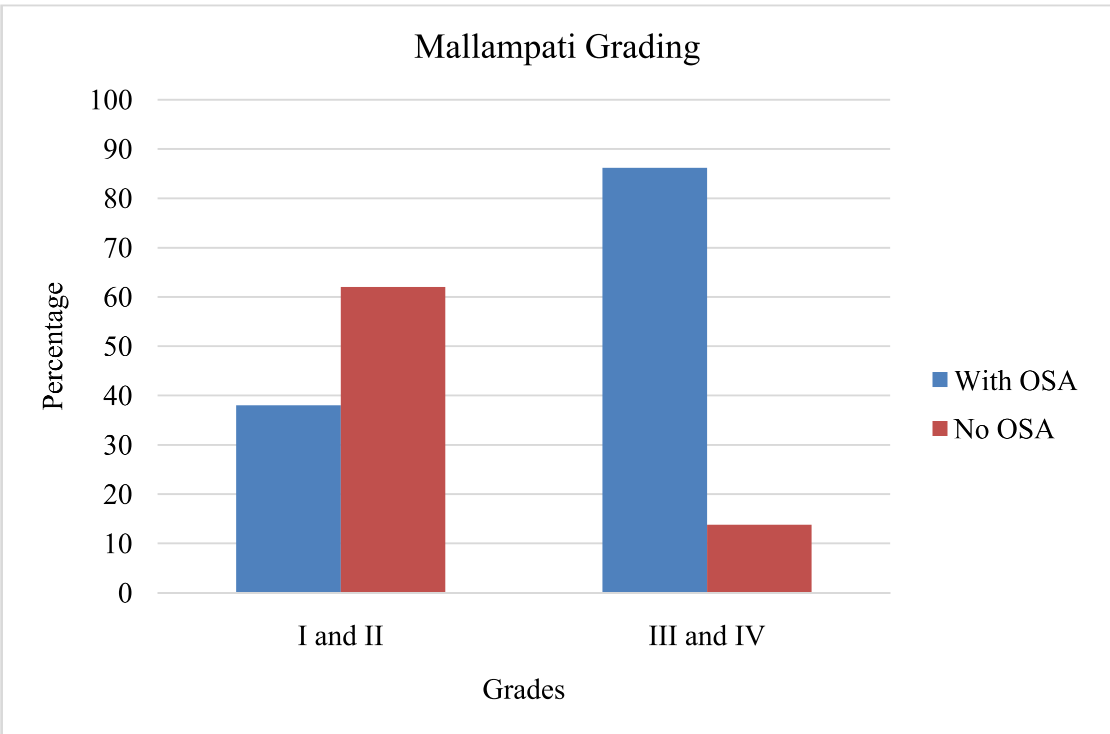


TABLE 14

TRIGLYCERIDES	WITH OSA	WITHOUT OSA	p-value[a]
<150	23 (65.7)	12 (34.3)	0.784
>150	46 (63)	27 (37)	

[a] Chi-square test was used to test the proportional difference between the different groups. p-value of 0.784 which is greater than the 0.05 level of signifies indicates that there is no significant association between triglycerides and the OSA Status.

Figure 20

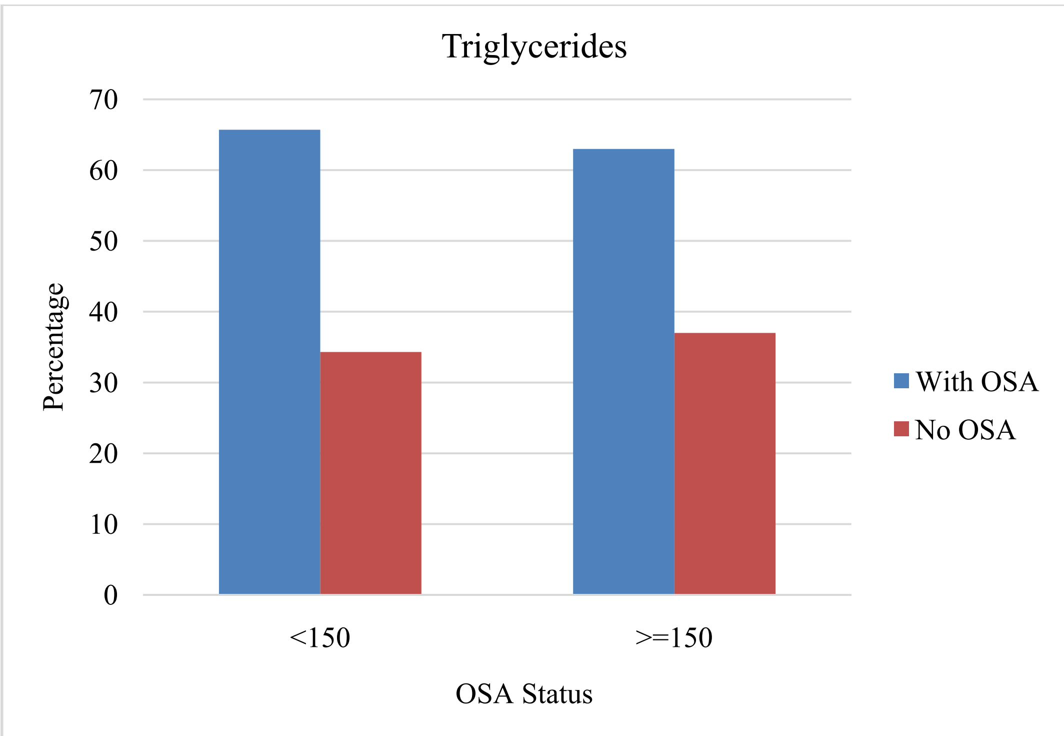


TABLE 15

HDL AMONG STUDY GROUP

HDL	WITH OSA	WITHOUT OSA	p-value[a]
<40 FOR MALES < 50 FOR FEMALES	51 (86.4)	8 (13.6)	<0.001
>40 FOR MALES >50 FOR FEMALES	18 (36.7)	31 (63.3)	

[a] Chi-square test was used to test the proportional difference between the different groups. p-value of <0.001 which is less than the 0.05 level of signifies indicates that there is a significant association between HDL and the OSA Status.

Figure 21

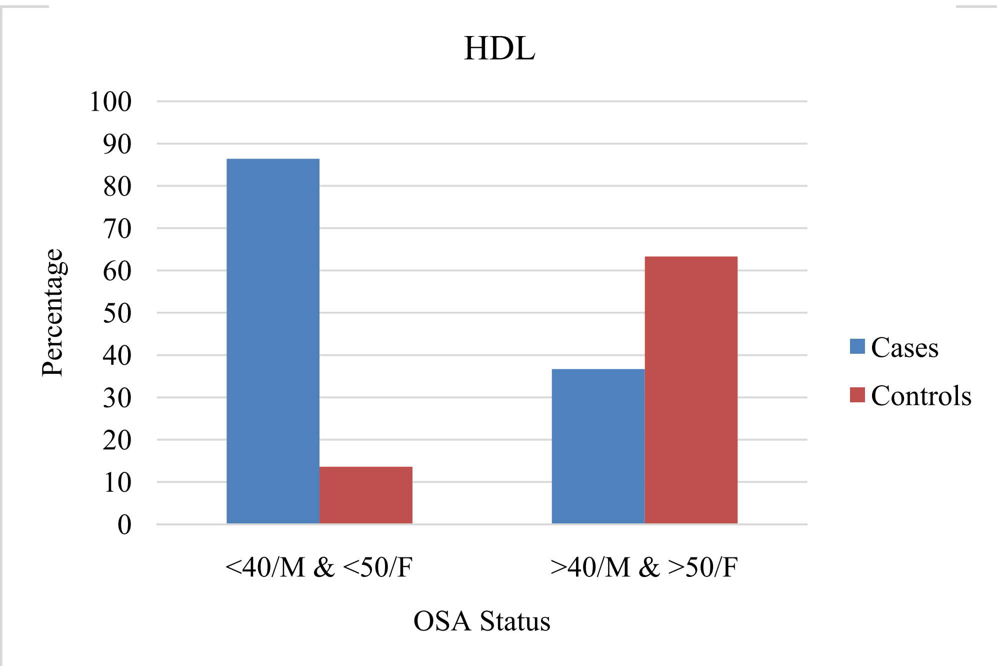


TABLE 16

Ahi and neck circumference

Neck Circumference	Ahi<5	Ahi>=5	p-value[a]
>43cms/M &>37cms/F	5 (9.1)	50 (90.9)	<0.001
<43cms/M &<37cms/F	44 (83)	9 (17)	

[a] Chi-square test was used to test the proportional difference between the different groups. p-value of <0.001 which is less than the 0.05 level of significance indicates that there is a significant association between Neck circumference and AHI.

Figure 22

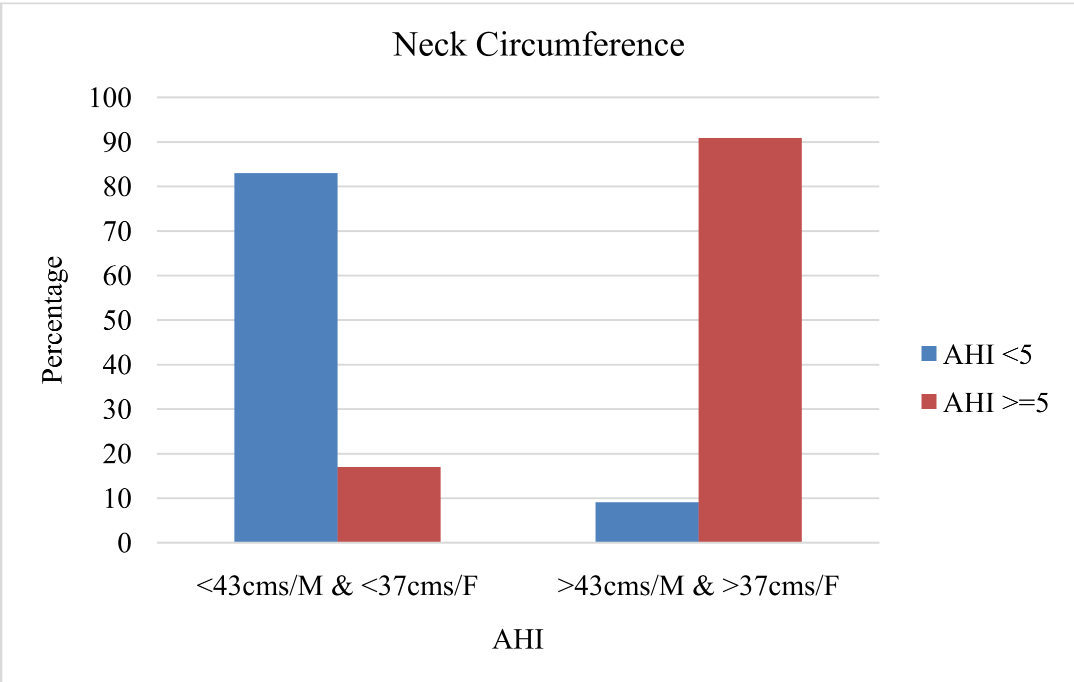


TABLE 17

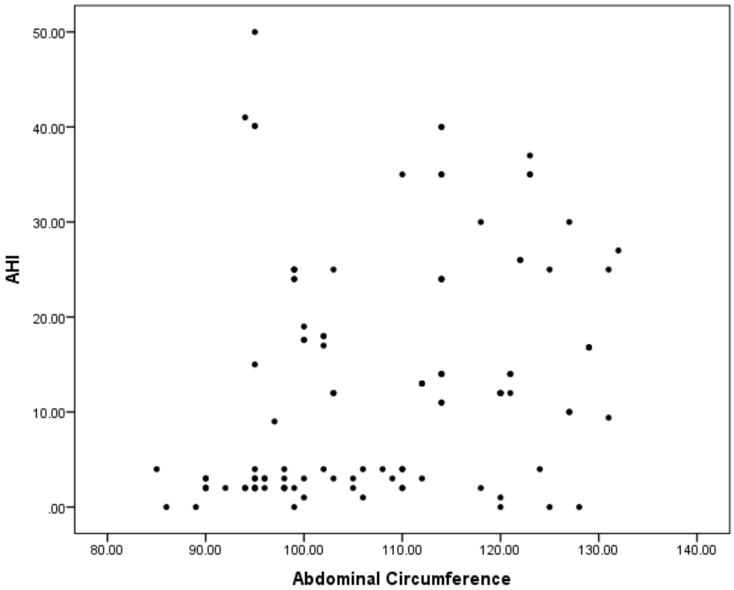
Ahi and abdominal circumference

Abdominal circumference	Ahi<5	Ahi>5	p-value[a]
>90 males &> 80 females	47 (44.3)	59 (55.7)	0.117
<90 males&<80 females	2 (100)	9	

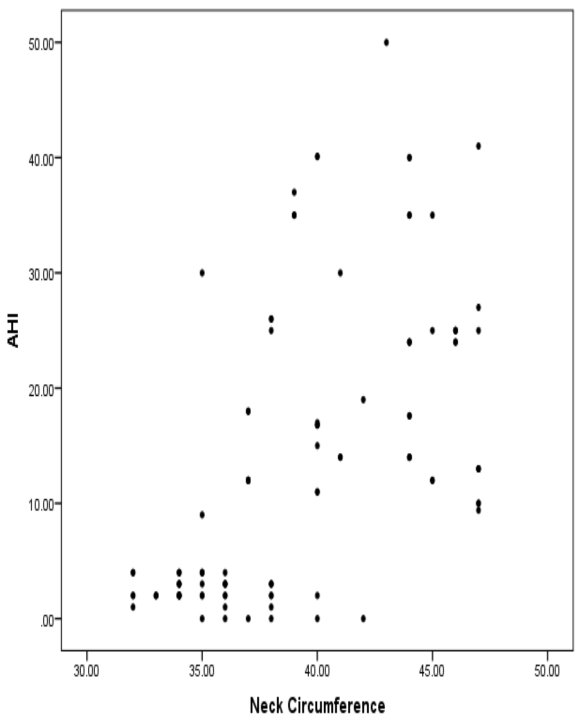
[a] Chi-square test was used to test the proportional difference between the different groups. p-value of 0.117 which is greater than the 0.05 level of signifies indicates that there is no significant association between abdominal circumference and AHI

Correlation of Anthropometric Measurements with AHI:

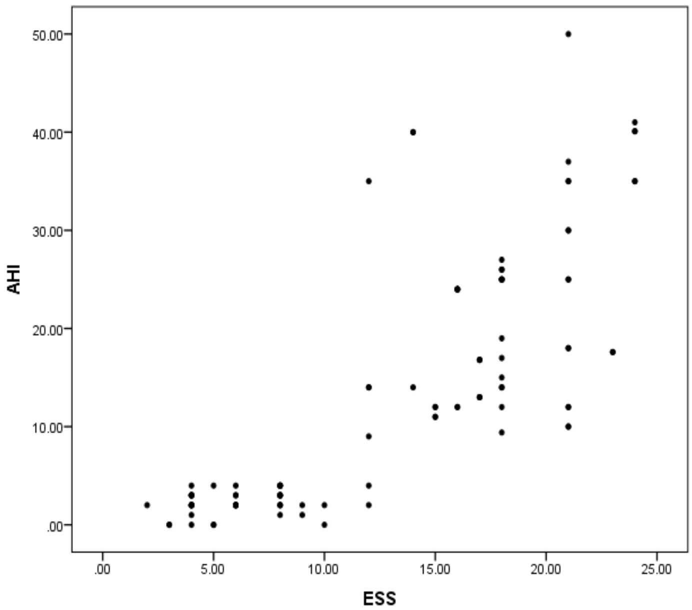
Correlation between Abdominal circumference and AHI is 0.355 with the p-value of <0.001.



Correlation between Neck circumference and AHI is 0.639 with the p-value of <0.001



Correlation between ESS and AHI is 0.830 with the p-value of <0.001.



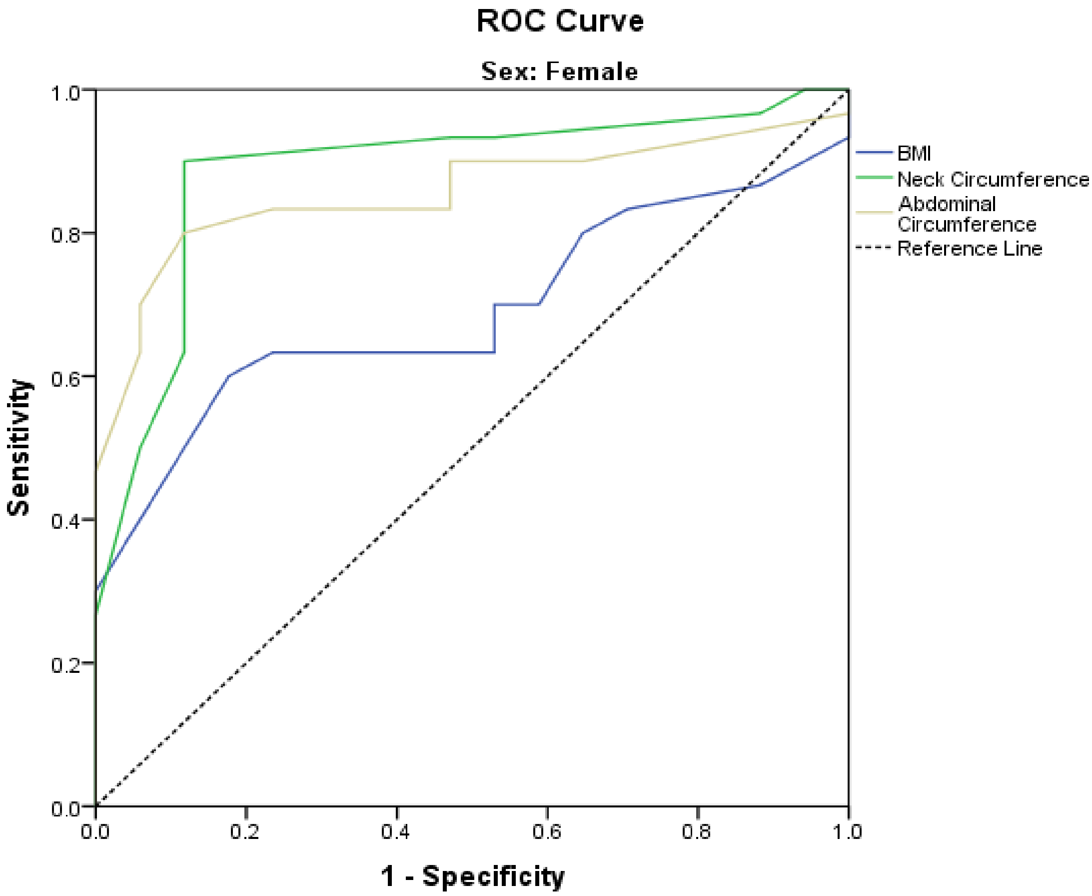
Comparison of anthropometric indices with AHI

TABLE 18

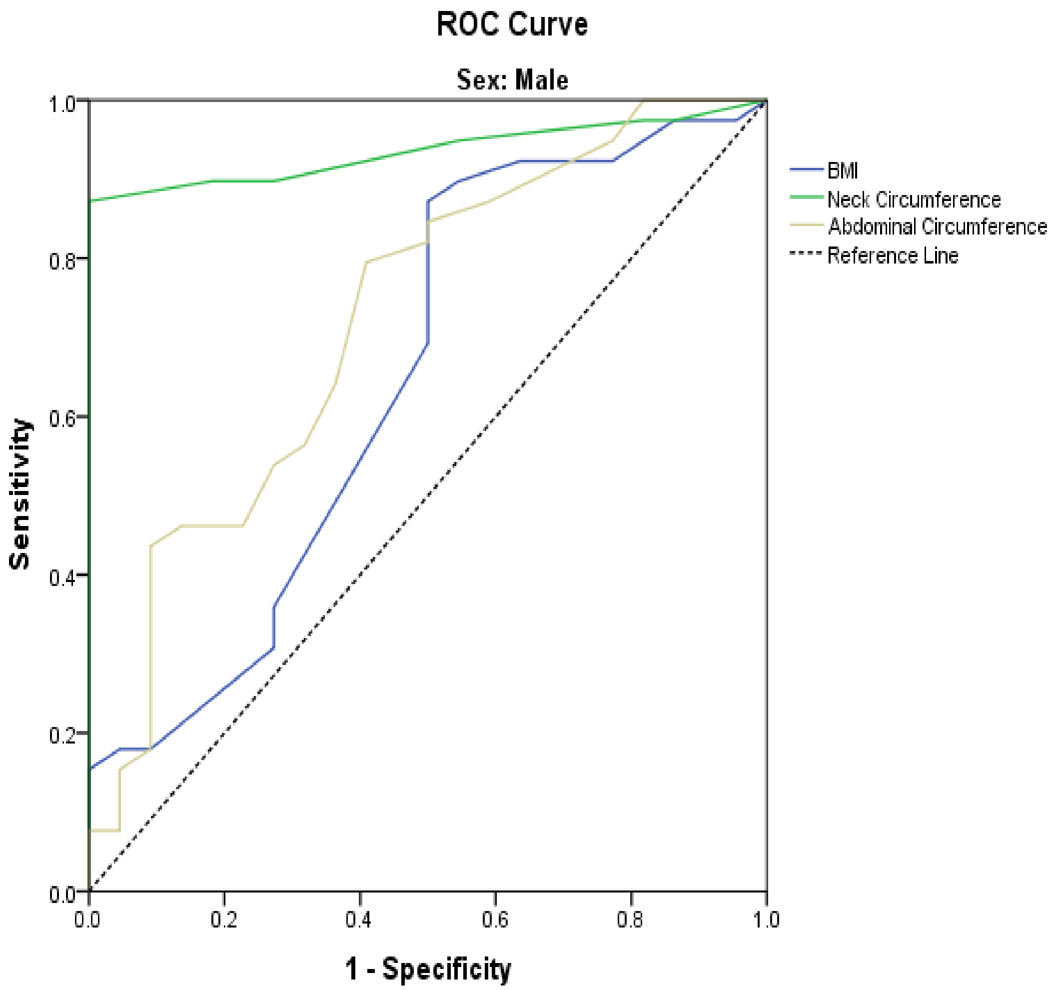
	Odds Ratio* (95% CI)	**p-value**
BMI	1.24 (1.08, 1.42)	0.003
Neck Circumference	1.87 (1.47, 2.40)	<0.001
Abdominal Circumference	1.11 (1.06, 1.16)	<0.001

Odds ratio for BMI and AHI was 1.24 and neck circumference odds ratio was 1.87 and odds ratio of abdominal circumference was 1.11 with both neck circumference and abdominal circumference has a p value of less than 0.001

ROC CURVE FOR FEMALES COMPARING BMI ABDOMINAL CIRCUMFERENCE AND NECK CIRCUMFERENCE WITH AHI SEVERITY



ROC CURVE FOR MALES COMPARING AHI WITH ABDOMINAL NECK CIECUMFERENCE AND BMI



STATISTICS OF ROC CURVE ANALYSIS

TABLE 19

	Neck circumference		Abdominal Circumference		BMI	
	Male	Female	Male	Female	Male	Female
Area Under the ROC Curve	0.935	0.886	0.724	0.857	0.648	0.691
Cut-off value	37	36	99.5	111	28.75	30.5
Sensitivity	0.897	0.900	0.641	0.800	0.872	0.633
Specificity	0.818	0.882	0.636	0.882	0.500	0.647

Statistics of ROC curve analysis

Neck circumference

Area under roc cure for males was 0.935 and females was 0.836. cut off value for neck circumference for males was 37and females was 36 and sensitivity and specificity was 89 and 81 for males and 90 and 88 for females

Abdominal circumference

Area under roc cure for males was 0.724 and females was 0.857.cut off value for neck circumference for males was 99.5 and females was 111.4 and sensitivity and specificity of 64 and 63 for males and sensitivity and specificity of females was 80 and 88 percent respectively.

BODY MASS INDEX

Area under roc cure for males was 0.648 and females was.0.691 cut off value for body mass index for males was 28.75 and females was 30.5 and sensitivity and specificity was 87 and 50 for males and 63 and 64 for females.

TABLE 20

Linear regression model to show the relationship of OSA status with various component of metabolic syndrome

Dependent variable	β (95% CI for β)	p-value
Waist circumference	9.515 (5.035, 13.996)	<0.001†
FBS	1.244 (-8.505, 10.993)	0.801
SBP	2.285 (-2.310, 6.879)	0.326
DBP	3.864 (0.782, 6.946)	0.015†
TG	12.807 (-9.174, 34.788)	0.251
HDL	-9.714 (-12.954, -6.475)	<0.001†
AHI	17.177 (13.167, 21.186)	<0.001†

Multiple Linear regression was used to assess the relationship. All the models were adjusted for Age and BMI. Beta coefficient along with its 95% CI is presented. Beta coefficient is interpreted as the average change in the dependent variable between subjects with and without OSA status.

† Significant correlation with OSA at 5% level of significance.

DISCUSSION

OSA is on increasing trend because of epidemic of obesity(1) In this study prevalence of metabolic syndrome was 57.4 percent among OSA group in south Indian hospital based population and 34.7 percent in the patients without OSA. Agarval et al reported prevalence of metabolic syndrome to be 79 percent in north Indian hospital based population.studY.(73)

Studies have shown increased prevalence of metabolic syndrome in north Indians compared to south Indians. (74) khan yesme et al have shown increased prevalence of metabolic syndrome among north indians and they are on increasing trend. The reason for difference in prevalence between north Indian study and our study may be because of that reason.

Population based studies has shown prevalence of metabolic syndrome in the Indian population to be 20 percent. Since our study is a hospital based study prevalence is slightly higher than those of population based studies.

Almost all these studies considered the variables involved in metabolic syndrome individually. Only a few investigations to date have evaluated the association of OSA with metabolic syndrome as a whole. Coughlin et al.23 in a sample of 61 men with OSA and 43 control subjects, found that OSA was independently associated with hypertension, high fasting glucose and triglyceride levels, low HDL-cholesterol level, and a trend toward high HOMA values, with an odds ratio of 9.1 for total metabolic syndrome.(76) However, they did not focus on the severity of OSA. Lam et al.[85] monitored 255 randomly selected Chinese volunteers for metabolic profile and sleep characteristics by overnight polysomnography and reported that OSA was associated with all the components of metabolic syndrome, and that metabolic syndrome was an independent predictor of OSA. The main value of the present study is our finding that with an increase in the severity of OSA, there is a significant increase in the prevalence of metabolic syndrome. In our study prevalence of metabolic syndrome in patients with mild osa is 50 percent, moderate osa is 88 percent and with severe osa is 100 percent and there is significant association between osa and metabolic syndrome.

Our study analyzed various anthropometric measures and their associations with the presence, as well as the severity, of OSA in the south indian adult population. To the best of our knowledge, this is the first study to determine the cut-off values for predicting the risk of OSA in anthropometric indices including, neck circumference, waist circumference, and body mass index, in an south indian population. In this study, patients with OSA had statistically significantly higher values of neck circumference waist circumference and body mass index compared to the patients without OSA. All of the anthropometric indices (NC, WC, and BMI) were significantly correlated with the severity of OSA. These results were similar to those of previous studies. Obesity, especially central obesity, is a major risk factor for OSA. simple anthropometric indices like waist cirumference, body mass index, and the neck circumference, are widely used as markers of obesity or central obesity. Clinically, neck circumference has been reported to be a useful predictor of OSA.

In our study, a logistic regression analysis showed that NC was a more potent predictor for the presence of OSA compared to WC and BMI.. scatter plot diagram also shows significant association of neck circumference with apnea hypopnea index compared with BMI and abdominal circumference. Neck circumference is a better predictor of apnea hypopnea index in both males and females. These results were similar to those of previous studies. Onat et al. [78] have reported that neck circumference contributes to metabolic syndrome more the waist circumference. Simpson and colleagues have evaluated the relationship between the severity of OSA and measures of regional obesity in a prospective observational study and found that neck circumference was significantly associated with OSA in both males and females.(77) Suhbey et al also demonstrated that neck cirmcumference is a better predictor of apnea hypopnea index severity.(78).

Genetic and environmental influences determine body fat distribution and obesity severity. The cut off values of anthropometric indices may vary differently according to sex and ethnicity Recently, neck circumference has been identified as an index of central obesity and a potential predictor of OSA This may be because of the fact that recent studies have shown that neck circumference is a better predictor of central obesity than other variables(81)

In our study ROC curve shows that neck circumference has better sensitivity and specificity in predicting apnea hypopnea index with sensitivity of around 90 percent and specificity of around 81 percent. Cizza et al. have reported that a neck circumference of ≥38 cm had a sensitivity of 54% and 58% and a specificity of 70% and 79% in predicting the presence of metabolic syndrome and OSAS, respectively [79]. Soylu et al.study shows that NC was a better predictor than waist circumference in determining OSA severity in Turkish adults (80). Accoerding to their study the optimal cut-off values of neck circumference for predicting OSA were 35.5 cm in females and 39 cm in males. Zhou et al. have reported that and that neck circumference values of 33 cm for females and 37 cm for males are the optimal cut-off values for metabolic syndrome in adults from China and states that neck circumference predicts cardio-metabolic risks beyond the other anthropometric indices (81)

hyeon hyi kang reported that the optimal cut-off values of NC for predicting OSA were 34.5 cm in females and 38.75 cm in males in Korean population. Despite ethnic differences these studies shows relatively similar cut off values for neck circumference. In our study predicting cut off values for neck circumference are 36 for females and 37 for males which is also similar suggesting neck circumference can be used universally beyond ethnic differences.

Martin et al. have reported that a BMI>30 kg/m^2 in both genders is associated with the development of OSA (82). Soylu et al. have shown that BMI values over 27.77 kg/m^2 in females and over 28.93 kg/m^2 in males increase the risk of OSA in a Turkish population (81) In the study by hyong he hyang et al, the cut-off value for BMI as an OSA determinant was over 23.05 kg/m^2 in females and over 24.95 kg/m^2 in males in a Korean population. In our study cut off values are 28.75 for males and 30.5 for males.(83)

Epsworth sleepiness score shows significant association with apnea hypopnea index and lower in patients with OSA compared to the patients without OSA. Our results are similar to the following studies. Lee sj et al reported a positive correlation between the ESS score and BMI, percentage of snoring time, minimum SpO(2) and time length of SpO(2) < 90%(84).Lowest desaturation was significantly associated with osa and may be that is the reason behind increased prevalence of metabolic syndrome variables. Ana safya et al have shown that there is a significant association between prevalence of metabolic syndrome and oxygen desaturation time.(82)

Mallampati grading shows significant association with the metabolic syndrome. Nuckton et al[30] prospectively assessed 137 patients attending a sleep clinic and reported an OR for OSA (defined as an AHI ≥ 5) of 2.5 (95% confidence interval [CI] 1.2-3.2) for each point increase in Mallampati class. The OR for Mallampati class was higher more than those of witnessed apneas and neck circumference. The authors concluded that the Mallampati class was a useful component of the clinical examination that had clinical value in predicting the presence of severity of OSA Our results are also similar to them. Hence mallampati grading can be used as a bedside assessment of patients with OSA.

We compared association of various variables of the metabolic syndrome with obstructive sleep apneA. of the various variables of metabolic syndrome like fasting blood glucose, blood pressure, hdl cholesterol and abdominal circumference diastolic blood pressure and hdl cholesterol shows significant association with metabolic syndrome with p value of less than 0.005. These results are similar to that of parish at al where their study shows significant relationship between hypertension and OSA and not other variables[(80)]

One study reported that the number of hypoxic episodes correlated with insulin resistance,[36] with another showing a modest correlation between AHI and fasting insulin, but not fasting blood glucose levels.[37] Some data shows a reduction in insulin resistance in obese patients with OSA and type 2 diabetes treated with CPAP,[38] whereas some found that while CPAP improved hypertension and daytime sleepiness, it will not alter insulin resistance.[39].With our data we can come to a hypothesis that OSA is not independently associated with fasting blood glucose.. Follow up studies are needed to arrive at a conclusion.

In our study there is significant association between OSA and HDL cholesterol. There are only 4 randomized studies[9,34–36] that evaluated lipid profile pre- and post- CPAP treatment in adults. With the exception of a clinical trial by Robinson et al., all studies involved a small sample size. Only Robinson et al. found a significant decrease in total cholesterol after CPAP, whereas three other studies did not find any changes in plasma lipids in response to therapy.(86) further studies with large sample size in the asian population is needed to come to a conclusion.

In our study OSA has been significantly associated with diastolic blood bressure. Baguet et al., using 24-hour ambulatory BP monitoring, exposed a substantial prevalence of OSAS-induced high BP occurring only during the night. Generally, high SBP is attributed to noncompliant, stiff arteries, whereas elevated DBP is related to the activation of the sympathetic autonomic nervous system. This augmented activity may be related to activation of chemoreceptors by intermittent hypoxia caused by the occurrence of apnea or hypopnea prior to the morning BP measurement. Furthermore, microarousals that usually end apnea events have also been implicated in the stimulation of sympathetic system, leading to BP elevation.(87)

The increasing prevalence of MS with increasi ng severity of OSA suggests an association of OSA with MS. However, obesity is a significant confounder in studies involving OSA and MS. Causative role cannot be inferred from this data alone, since, it is a common major risk factor for both conditions. 40-90 per cent obese individuals have Obstructive sleep apnea and about 70 per cent of Obstructive sleep apnea patients have obesity, Only a longitudinal study would be able to definitely prove whether Obstructive sleep apnea precedes and causes metabolic syndrome or vice versa, and whether obesity is a predisposing factor for both these conditions.

CLINCAL IMPLICATIONS OF THE STUDY

The clinical implications are that there is a high prevalence of metabolic syndrome in patients presenting to sleep clinics with symptoms suggestive of Obstructive sleep apnea, irrespective of whether they have obstructive sleep apnea or not. Simple indices like neck circumference, mallampati scoring and epsworth sleepiness score will help in accessing the severity of OSA and hence metabolic syndrome.

The prevalence of MS is even higher if they have obstructive sleep apnea. Metabolic syndrome and its components are more likely to be present in patients with obstructive sleep apnea and its prevalence will increase with increasing severity of obstructive sleep apnea.

Screening for metabolic syndrome and its components along with the work up of obstructive sleep apnea will allow early detection of these cases. This relationship of metabolic syndrome with obstructive sleep apnea can also explain the mechanism for increased mortality in patients with OSA.

LIMITATIONS OF STUDY

The present study has some limitations. Being a hospital-based study there was referral bias with more symptomatic patients with sleep disturbances likely to be referred to our hospital.

The non-OSA group did not reflect absolutely normal healthy individuals and they were more likely to have components of metabolic syndrome like hypertension, diabetes, dyslipidaemia and obesity than healthy volunteers. However, this will decrease the difference found between the two groups rather than increase it.

For an important potential confounder obesity, matching was not done. An ideal study design must have BMI matched controls to reduce confounding..

STRENGTHS OF THE STUDY

The strengths of the present study include

(i) a large sample size of 108 patients

(ii) OSA in control group has been excluded by performing a full overnight polysomnography study in each one of them;

(iii) obstructive sleep apnea has been diagnosed by level 3 study in all

(iv) use of AHI cut-off of ≥5 events/h in accordance with the results of the Sleep Heart Health Study

(v) inclusion of both males and females in the study so that can be applied to both groups

CONCLUSION

In conclusion, our study showed that the prevalence of metabolic syndrome was higher in patients of OSA than controls the prevalence increased with increasing severity of OSA.

Of the variable parameters of metabolic syndrome diastolic BP and HDL cholesterol shows significant association with metabolic syndrome. Further follow up studies are needed to come to a conclusion.

Of the various anthropometric indices neck circumference shows significant correlation with metabolic syndrome. The cut off values of neck circumference are 36 for females and 37 for males. the cut off values of abdominal circumference are relatively same in different studies despite ethnic differences.

ROC curves shows neck circumference has better sensitivity and specificity than other anthropometric indices like body mass index and abdominal circumference. Mallamapati scoring and epsworth sleepiness score also shows significant association with OSA.

Hence we recommend that simple indices like neck circumference, mallampati scoring and epsworth sleepiness score must be done for all patients attending OPD with sleep disturbances and patients with OSA should be investigated for MS and vice versa, as early detection and correction may result in significant decrease in morbidity and mortality.

Even simple life style changes and behavorial changes will produce a great impact. CPAP treatment will cause significant reduction in cardiovascular mortality. Hence routine screening will help in diagnosing early and preventing many complications.

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ABBREVATIONS

AHI	-	apnea hypopnea index
AC	-	abdominal circumference
CPAP	-	continous positive airway pressure
DBP	-	diastolic blood pressure
NC	-	neck circumference
OSA	-	obstructive sleep apnea
OSAS	-	obstructive sleep apnea syndrome
ROS	-	reactive oxygen species
SBP	-	systolic blood pressure
WC	-	waist circumference

URKUND

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The combination of obstructive sleep apnea and metabolic syndrome has been termed as syndrome z .Sleep related breathing disorders and metabolic syndrome are on increasing trend because of epidemic of obesity.(1) Beyond their epidemiologic relationship, growing evidence suggests that OSA may be causally related to metabolic syndrome.

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The combination of metabolic syndrome and obstructive sleep apnea (OSA) has been termed "syndrome Z." The prevalence of both OSA and metabolic syndrome is increasing worldwide, in part linked to the epidemic of obesity. Beyond their epidemiologic relationship, growing evidence suggests that OSA may be causally related to metabolic syndrome.

Its prevalence varies from 74 to 85% among patients with obstructive sleep apnea and from 37 to 41% among patients with nonobstructive sleep apnea.(2)

Metabolic syndrome

The

National Cholesterol Education Program Adult Treatment Panel III (NCEP

ATP III)

report2 defines metabolic syndrome as three or more of the following five variables: hypertension, increased fasting blood glucses, low high-density lipoprotein cholesterol (HDL-C), elevated serum triglyceride, and abdominal obesity. (3) \

Obstructive sleep apnea Obstructive sleep apnea syndrome is characterized by repetitive episodes of upper airway obstruction

that occur during sleep, usually associated with a reduction in blood oxygen saturation.(4) Structural factors like increased volume of tongue lateral pharyngeal wall and soft tissue are significant risk factorsr osa and osa patients have small anatomically pharyngeal airways.(5).

During wakefulness there will be increased pharyngeal dilator muscle activity due to long time neuromuscular compensation and that will be reduced dring sleep in patients with osa combined with reduced reflex activity of muscles during sleep causes airway collapse in apneic patients. This can lead to a combination of hypopneas, or reduction in airflow associated with a fall in oxygen saturation, or apneas, or complete cessation of airflow.(6)

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **“TO INVESTIGATE THE PREVALENCE AND ASSOCIATION OF METABOLIC SYNDROME AND ITS COMPONENTS IN PATIENTS WITH OSA AND WITHOUT OSA-A HOSPITAL BASED CROSSSECTIONAL STUDY”** of the candidate **Dr. C. SUGANYA** with registration number **201627003** for the award of MD in the branch of Tuberculosis & Respiratory diseases. I personally verified the urkund.com website for the purpose of plagiarism check. I found that uploaded thesis file contains from introduction to conclusion pages and result shows **6** percentage of plagiarism in the dissertation.

Guide & supervisor sign with seal

INSTITUTIONAL ETHICS COMMITTEE
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EC Reg.No.ECR/270/Inst./TN/2013
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CERTIFICATE OF APPROVAL

To
Dr.Suganya.C.
I Year PG in MD TB&CD
Institute of Thoracic Medicine/
Madras Medical College
Chennai 600 003

Dear Dr.Suganya.C,

The Institutional Ethics Committee has considered your request and approved your study titled **"TO INVESTIGATE THE ASSOCIATION AND PREVALENCE OF METABOLIC SYNDROME AND ITS COMPONENTS IN PATIENTS WITH OSA – A HOSPITAL BASED CROSS SECTIONAL STUDY " - NO.27032017(I)**

The following members of Ethics Committee were present in the meeting hold on **02.03.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr. K.Narayanasamy,MD,DM.,Dean(FAC), MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.S.Suresh, MS, Prof. of Surgery,MMC,Ch-3	: Member
5.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
6.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
7.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

PATIENT CONSENTFORM

Study Detail : “**TO INVESTIGATE THE ASSOCIATION OF METABOLIC SYNDROME AND ITS COMPONENTS IN PATIENTS WITH AND WITHOUT OSA**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient’s Name :

Patient’s Age :

Identification Number:

Patient may check (√) these boxes :a) I confirm that I have understood the purpose of procedure for above study. I have the opportunity to ask question and all my questions and doubts have been answered tomy complete satisfaction. ❏

b) I understand that my participation in study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❏

c) I understand that sponsor of the clinical study, others working on the sponsor’s behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as

required under the law. I agree not to restrict the use of any data or results that arise from this study. ❏

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❏

e) I hereby consent to participate in this study. ❏

f) I hereby give permission to undergo detailed clinical examination, Radiographs,blood investigations and other procedures as required. ❏

Signature/thumb impression of patients/patients attendar

Signature of Investigator:

patient’s Name and Address:

Study Investigator’s Name: **Dr.Suganya C**

EVALUATION FORM

Name:
Age:
Sex:
OP/Ip number:
Presenting complaints:

History of presenting illness:

Past history:

Treatment history:

Smoking history:

Personal history:

Occupational history:

CO-MORBIDITY:

General examination:

Body Mass Index:

Waist circumference:

Neck circumference

Blood pressure:

Systemic examination:

Blood investigations:

COMPLETE BLOOD COUNT

RFT, LFT

RBS,FBS,PPBS

Fasting Lipid profile: triglyceride level

LDL cholestrol

HDL cholesterol:

ECG

Echocardiography:

Polysomnography

s no	AGE	SEX	BMI	NECK CIRC	ABD CIR	ESS	AHI	LOWEST DESATURATION	TRIG	HDL	systolic	FBS	MS	dias bp	mallambati
1	57	F	40	38	125	21	25	52	118	38	140	129	YES	90	3
2	40	M	26	35	118	21	30	36	85	25	100	196	NO	60	2
3	40	F	33	38	122	18	26	39	300	24	140	62	NO	90	4
4	42	M	29	44	114	24	35	64	439	26	120	96	NO	82	3
5	45	M	30	46	99	18	25	82	85	35	130	114	YES	80	2
6	53	M	30	44	114	16	24	49	250	35	150	145	YES	90	1
7	55	F	40	47	112	17	13	53	159	40	140	150	YES	110	3
8	34	M	34	44	100	23	17.6	91	171	30	120	74	NO	80	4
9	37	M	29	47	94	24	41	61	259	40	120	83	NO	80	2
10	40	F	23	36	86	3	0	97	159	40	120	79	NO	74	3
11	40	F	40	38	125	5	0	97	118	38	140	129	YES	90	4
12	50	F	29.7	37	102	21	18	87	118	38	140	91	YES	90	4
13	49	F	35	37	120	15	12	50	230	24	110	128	YES	80	3
14	43	F	34	37	120	21	12	87	150	37	130	117	YES	85	3
15	48	F	35	40	114	15	11	92	179	38	140	83	YES	90	3
16	41	F	33	40	129	17	16.8	84	154	42	110	91	YES	90	4
17	42	M	34	47	131	21	25	83	125	38	130	93	YES	90	2
18	40	M	30.5	44	114	14	40	60	170	35	140	110	YES	90	4
19	35	M	29	39	123	21	35	52	181	44	140	106	YES	90	3
20	30	F	28	47	127	21	10	75	200	42	130	105	YES	90	2
21	55	M	30	45	103	16	12	87	160	44	140	86	YES	90	4
22	57	M	31	40	95	24	40.1	83	160	35	140	110	YES	90	3
23	48	F	33	41	121	18	14	85	160	60	140	140	YES	90	4
24	48	M	34	44	114	12	14	87	170	38	135	110	YES	90	3
25	45	M	30	46	99	16	24	92	210	35	135	110	YES	90	4
26	45	M	30	42	99	5	0	92	170	35	140	120	YES	90	2
27	41	F	32	40	128	4	0	93	154	42	130	125	YES	90	3
28	44	M	33	47	131	18	9.4	93	164	38	130	95	YES	90	4
29	48	F	34	37	120	3	0	92	163	37	130	94	YES	90	3
30	42	M	26	47	132	18	27	82	140	43	110	97	NO	80	2
31	43	F	27	37	121	18	12	84	140	52	110	93	NO	80	1
32	55	M	28	45	103	18	25	86	145	43	110	93	NO	80	4
33	48	F	26	41	127	21	30	87	160	35	130	97	YES	100	3
34	50	F	28	40	95	18	15	95	140	47	110	97	NO	80	4
35	36	M	29	39	123	21	37	67	170	40	130	110	YES	90	3
36	48	M	35	44	114	14	14	92	140	45	110	96	NO	80	4
37	33	M	30	35	97	12	9	96	141	45	110	83	NO	80	3
38	48	F	24	40	129	17	16.8	84	154	42	140	93	YES	90	3
39	40	m	25	38	99	12	2	93	130	45	125	75	n0	70	2
40	35	m	28	38	100	9	1	96	128	45	123	75	no	76	3

41	52	f	27	40	110	9	2	96	145	45	140	106	no	80	2
42	32	m	26.5	33	92	8	2	90	150	42	110	86	no	70	1
43	50	f	27.5	33	90	6	2	98	160	55	120	103	no	80	2
44	40	m	24.5	34	94	6	2	95	142	42	120	120	no	80	1
45	31	m	31	32	98	4	2	96	120	58	110	95	no	70	3
46	40	f	26	34	110	8	4	98	130	55	120	96	no	80	2
47	40	m	28.5	38	96	4	3	98	145	45	120	124	n0	76	2
48	48	f	31	34	109	4	3	98	150	55	130	85	no	90	2
49	40	m	27	35	98	6	4	97	155	38	120	96	no	80	2
50	43	f	29	36	98	8	3	97	160	55	120	86	no	80	2
51	46	m	30	34	95	6	2	98	155	55	####	106	yes	90	2
52	50	f	26	34	112	8	3	98	186	36	150	170	yes	90	2
53	56	m	25	35	85	8	4	98	165	50	135	86	no	90	2
54	45	f	27	34	90	4	2	98	155	45	120	85	no	75	2
55	50	m	26	35	95	8	3	98	167	55	110	86	no	70	1
56	46	f	27	32	106	4	1	98	178	50	110	107	no	70	1
57	50	m	30	38	110	2	2	98	176	50	140	117	yes	90	1
58	48	f	33	34	95	8	2	98	167	55	130	76	no	80	1
59	47	m	27	34	90	6	3	98	165	56	126	85	no	82	1
60	43	m	28	35	102	4	4	98	175	58	124	76	no	82	2
61	45	f	30	36	95	8	2	98	220	35	135	150	no	90	2
62	46	f	28	36	100	4	3	98	165	55	120	76	no	80	2
63	50	m	31	34	105	6	2	98	155	55	120	89	no	76	3
64	48	f	30	36	95	8	3	98	165	55	120	72	no	80	4
65	49	m	26	34	95	4	2	98	145	54	125	78	no	80	2
66	43	f	30	36	90	8	3	98	155	56	140	80	no	90	2
67	46	m	32	35	96	4	2	98	165	55	124	112	no	78	3
68	42	f	33	38	105	4	3	97	165	40	135	120	yes	80	3
69	43	m	30	32	124	8	4	96	175	42	140	130	yes	90	2
70	44	m	31	36	118	10	2	98	155	45	135	123	yes	80	2
71	35	f	32	34	106	12	4	98	180	50	136	107	yes	86	2
72	36	m	31	36	108	8	4	98	175	40	120	108	yes	75	2
73	37	m	30	34	103	6	3	97	178	55	135	120	yes	90	2
74	38	f	34	35	98	4	2	96	180	35	120	140	yes	80	1
75	37	m	33	32	95	5	4	95	176	50	134	90	yes	90	3
76	42	f	31	36	120	8	1	99	135	40	130	130	yes	96	2
77	48	m	30	35	89	10	0	98	132	55	110	170	yes	100	3
78	39	m	29	42	100	18	19	94	158	38	140	125	yes	80	3
79	50	m	31	45	110	12	35	90	160	20	150	106	yes	90	3
80	40	m	31	43	95	21	50	86	130	39	130	120	yes	84	3
81	38	m	30	40	102	18	17	90	128	38	150	94	yes	86	3
82	40	F	33	38	122	18	26	39	300	24	140	62	NO	90	4
83	42	M	29	44	114	24	35	64	439	26	120	96	NO	82	3

84	45	M	30	46	99	18	25	82	85	35	130	114	YES	80	2
85	53	M	30	44	114	16	24	49	250	35	150	145	YES	90	1
86	55	F	40	47	112	17	13	53	159	40	140	150	YES	110	3
87	34	M	34	44	100	23	17.6	91	171	30	120	74	NO	80	4
88	50	f	27.5	33	90	6	2	98	160	55	120	103	no	80	2
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102	35	M	29	39	123	21	35	52	181	44	140	106	YES	95	3
103	30	F	28	47	127	21	10	75	200	42	130	105	YES	100	3
104	55	M	30	45	103	16	12	87	160	44	140	86	YES	90	4
105	57	M	31	40	95	24	40.1	83	160	35	140	110	YES	90	4
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107	48	M	34	44	114	12	14	87	170	38	135	110	YES	90	3
108	45	M	30	46	99	16	24	92	210	35	135	110	YES	90	4